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Pharmacokinetics and toxicity of 5-day continuous infusion of vinblastine

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Summary. *Ten patients with advanced cancer were treated in a phase-I trial with monthly cycles of a 5-day infusion of vinblastine. Serum drug levels were relatively constant after 24 h and there was no correlation between drug level and myelosuppression or toxicity. Previously underscribed toxicities were observed, including one hypersensitivity reaction and three cases of severe, only slowly reversible, sensorimotor neuropathy. Two patients showed objective tumor regression during the vinblastine infusion therapy.*

Introduction

The antineoplastic effect of vinblastine sulfate is attributed to its ability to bind to cellular microtubules and inhibit cell division. This effect takes place mainly in late S-phase, making the drug relatively cell-cycle-specific [2]. Vinblastine is traditionally given as an IV bolus injection, and the pharmacokinetics of a bolus injection of the drug have been thoroughly studied [5, 6]. Vinblastine is largely cleared from the serum within minutes, and there is significant binding to white blood cells, platelets, and other tissues.

Several investigators have recently begun clinical trials of prolonged infusions of vinblastine and other vinca alkaloids, hypothesizing that greater cell kill may be achieved if a larger fraction of the tumor cells are given the opportunity to enter S-phase during drug exposure [1, 3, 4, 10]. In a phase-II trials of a 5-day continuous infusion of vinblastine for advanced breast cancer, Yap et al. [10] reported a 40% response rate with modest toxicity at doses of 1.6–2.0 mg/m^2/24 h. Preliminary data suggest that vindesine, a vinca alkaloid with pharmacokinetics similar to that of vinblastine, may be most efficacious when administered as a constant infusion [1].

The present study was designed as a phase-I study of a 5-day continuous infusion of vinblastine in patients with advanced cancer. The goals of the study were to define the toxicity and tolerated dose range of the infusion, and to describe its pharmacokinetics.

Materials and methods

Patient eligibility. Patients with histologically documented advanced malignancy who had exhausted all standard curative and palliative therapy were accepted for study. All patients had an expected survival of 2 months and an ECOG performance status of 3 or better. Adequate bone marrow, renal, and hepatic reserve were required, as defined by the following laboratory criteria: WBC $> 4{,}000/mm^3$, platelet count $> 100{,}000/mm^3$, serum creatinine < 1.5 mg/dl, serum serum bilirubin < 1.5 mg/dl, and serum SGOT $<$ twice normal. Patients with significant myelopathy and neuropathy were excluded, but symptomatically stable brain metastasis did not mandate exclusion.

Drug therapy. Vinblastine sulfate (Velban, Eli Lilly and Co.) was given through a central venous catheter as a 5-day continuous infusion. The daily dose was mixed in 1.0 l of 5% dextrose and water and infused at a rate of 42 cm^3/h using an IVAC pump. The initial patients were treated at a dose of 1.25 mg/m^2/24 h. After three patients had been treated at a given dose level without severe toxicity, for the next patient the dose was escalated by an increment of 0.25 mg/m^2/24 h. Individual patients were eligible for dose escalation by an identical increment if the nadir white blood cell count during the preceding cycle was greater than $2{,}000/mm^3$ and non-marrow toxicities were acceptable.

Vinblastine serum levels. Serum samples were taken before each infusion and at 8 h, 24 h, 48 h, 72 h, 96 h, and 120 h after the start of the infusion. Samples were allowed to clot, centrifuged, labeled, and frozen for storage at −70° C. Vinblastine radioimmunoassay was performed according to a method described previously [8], using commercially available radiolabeled vinblastine (^{3}H-vinblastine sulfate, Amersham) and rabbit vinblastine antiserum (kindly provided by Dr M. A. Root of the Lilly Research Laboratory).

Results

Patient characteristics

Ten patients received a total of 19 cycles of vinblastine infusion therapy (1–4 cycles per patient) before protocol accrual was closed due to unexpected toxicity. Table 1 details the characteristics of the patients entered.

Toxicity

Table 2 describes the pattern of myelosuppression observed at the doses employed. One patient was hospitalized with septicemia associated with leukopenia, and two other treatment cycles were associated with central venous catheter-related septicemia. No significant myelosuppression was observed by day 5 of the infusion. Nadir myelosuppression was

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Table 1. Patient characteristics (10 patients)

Median age (years)	60 (range: 49–67)
Sex (male/female)	6/4
Primary tumor type	
Small cell lung carcinoma	3
Adenocarcinoma lung	2
Renal cell carcinoma	2
Adenocarcinoma, ovary	1
Adenocarcinoma, sweat gland	1
Lymphoma	1
Previous therapy	
None	2
Combination chemotherapy	8
Radiation therapy	7
Neurological history	
Brain metastasis	3
Brain radiotherapy	4
Vincristine/etoposide chemotherapy	3
Stroke	1
Peripheral neuropathy or myelopathy	0

Table 2. Myelosuppression at doses studied

Dose ($mg/m^2/24$ h)	No. of patients	Mean (range) nadir of WBC/mm^3	Mean (range) platlets $\times 10^3/mm^3$
1.25	3	5.3 (4.1–6.6)	255 (32–429)
1.50	6	6.2 (2.8–13.1)	186 (65–308)
1.75	4	1.6 (0.4–2.8)	140 (66–208)
2.00	1	1.5	175

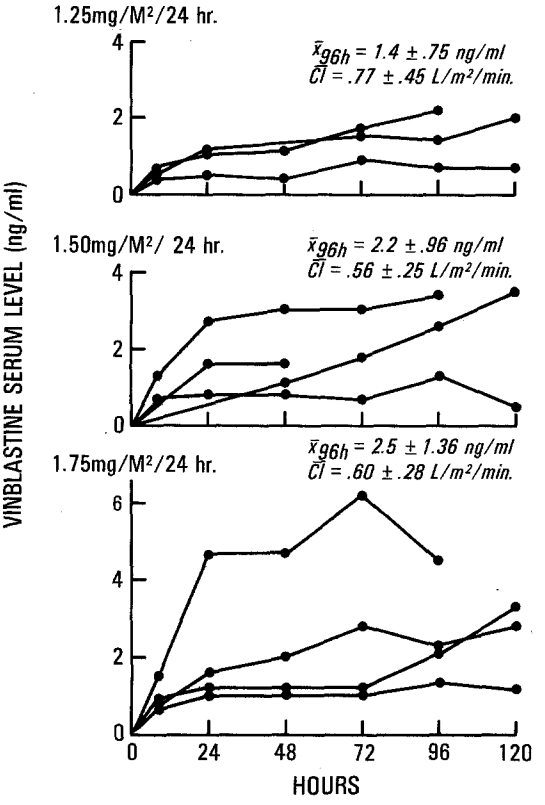

Fig. 1. Vinblastine serum level by dose ($\bar{x}$ 96 h, mean serum vinblastine level at 96 h; $\overline{CI}$, mean total body vinblastine clearance)

observed at approximately day 14 in most patients. As shown in Table 2, leukopenia was reliably produced by a dose of 1.75 $mg/m^2/24$ h in our heavily pretreated group of patients.

Nausea, vomiting, and alopecia were not observed. Two patients complained of constipation. One patient had an allergic reaction necessitating discontinuation of therapy on day 3 of his infusion. This was characterized by respiratory distress and a maculopapular rash. The symptoms disappeared after stopping the vinblastine and instituting supportive care, but they reappeared the following day when the vinblastine infusion was resumed.

The most significant toxicity in this series was the development of apparent neuropathy in three of the patients. One patient developed burning paresthesias of his hands and feet, postural hypotension, and mild objective motor weakness. The other two patients had mild peripheral sensory loss coupled with severe motor weakness most pronounced in proximal muscle groups. Both of these patients had slow improvement of their weakness after the drug was stopped, but one remained bedridden until she succumbed with progressive disease.

Response

One patient with lung adenocarcinoma and one patient with hypernephroma had partial regressions (PRs) after one cycle of vinblastine infusion therapy. The patient with lung cancer had therapy discontinued after two cycles because of neurologic toxicity and subsequently showed rapid disease progression. In the patient with hypernephroma, the PR lasted 5 months. The remainder of the treated patients had either steady disease progression or transient stabilization followed by progression.

Pharmacokinetics

Figure 1 displays the pharmacokinetic data. Adequate data were available at three doses: 1.25 $mg/m^2/24$ h, 1.50 $mg/m^2/24$ h, and 1.75 $mg/m^2/24$ h. As shown, a relatively stable serum drug level is attained between hours 24 and 120 of the infusion. There is substantial variation between patients in the plateau drug level achieved, and consequently there is overlap between the range of levels achieved with the doses studied. There was no apparent correlation between plateau drug level and degree of myelosuppression or toxicity. The mean total body vinblastine clearance for all patients studied was 0.63 ± 0,30 $l/m^2/min$. Clearance was not significantly different at the infusion rates studied.

Discussion

The pharmacokinetics of a 5-day vinblastine infusion have not been described previously. Our results suggest that in the tolerated dosage ranges, vinblastine serum levels of 1–4 ng/ml are achieved by 24 h and plateau in that range for the duration of the infusion. These results are similar to those obtained by Hande et al. [3], in a study of a 48-h infusion of vindesine. Nelson et al. [5] studied the pharmacokinetics of a single bolus injection of vinblastine and found that although serum levels dropped very significantly within minutes after injection,

detectable levels of 1–2 ng/ml were present 48 h later. Our finding of comparable serum levels of vinblastine in a biologically active dose range on the 5-day infusion schedule suggests that similar pharmacologic and antineoplastic results might be achieved by an intermittent bolus dosing schedule. This hypothesis is supported by Schulman et al. [7], who documented activity for a 48-h divided-dose vinblastine schedule.

In the study of Yap et al. [10], in which a 5-day vinblastine infusion was used for patients with advanced breast cancer, no significant toxicities other than dose-related myelosuppression were reported. The present results confirm the observation that leukopenia is consistently observed 7–14 days following initiation of a 5-day vinblastine infusion of 1.75 mg/m^2/24 h. For future phase-II trials of this treatment schedule, we recommend a starting dose of 1.5 mg/m^2/24 h, with dose escalation as tolerated, based upon the nadir WBC.

Two previously unreported toxicities of vinblastine infusion were encountered during the study. One patient had a probable hypersensitivity reaction to the drug. Three others had significant, disabling neurological toxicity. There are several features common to the patients with neurotoxicity. All three had lung cancer (two with small cell histology, one with adenocarcinoma), and two of the three had brain metastasis. One patient with and one patient without brain metastases had had prior CNS irradiation. Two of the patients had had prior chemotherapy with vincristine and etoposide. The neurotoxic complications of vincristine are well-known, and treatment with both vincristine and etoposide may cause severe neuropathy in some patients [9]. Five-day vincristine infusion is believed to cause more neuropathy than a conventional bolus schedule [4]. While recognizing that the symptoms observed in our patients were relatively nonspecific and could possibly have been due to other, non-drug-related factors (i.e., paraneoplastic syndrome and/or brain metastasis), we believe they were directly related to the vinblastine infusion therapy. It is possible that patients with brain metastasis, prior or concurrent brain irradiation, or prior therapy with neurotoxic drugs may be at increased risk for neurologic toxicity with 5-day vinblastine infusion.

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