Pharmacokinetics of Vindesine Given as an Intravenous Bolus and 24-Hour Infusion in Humans

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ABSTRACT

The pharmacokinetics of vindesine was examined after the determination of serum drug levels by radioimmunoassay in patients who received the drug either as an i.v. bolus or a 24-hr infusion. After i.v. bolus, vindesine was eliminated from the serum by triphasic decay. The central compartment was approximately 6 times the serum volume. The peak serum level achieved by i.v. bolus was approximately 16 times that achieved by the 24-hr infusion. The post-24-hr-infusion serum decay followed biphasic decay. Pharmacokinetic modeling, assuming a prolonged infusion period, resulted in a triphasic decay curve, with an extremely short distribution phase which would not be clinically detectable. This was due to the incorporation of the distribution phase into the infusion period. This explains the experimental data of a biphasic decay curve observed after 24-hr infusion. Pharmacokinetic parameters for the two phases observed after 24-hr infusion were similar to values calculated from i.v. bolus data. The c x t for 24-hr infusion identical to that after i.v. bolus; theoretically, the c x t appears constant regardless of infusion time. It is concluded that the rate of elimination and/or the c x t, rather than the peak serum level, played a role in the degree of hematological toxicity.

INTRODUCTION

VDS3 is a new synthetic antineoplastic agent derived from the Vinca alkaloid vinblastine sulfate. Clinical studies have been carried out in various institutions in the United States and Europe (1, 3, 6, 7, 10, 14, 19). In our Phase I study of VDS, human dose findings were done in 2 schedules, i.v. bolus and 24-hr infusion administered weekly. Major clinical side effects observed after i.v. bolus and 24-hr infusion were myelosuppression and neurotoxicity. At identical dosage levels, degrees and parameters of toxicity were indistinguishable (14).

During our Phase I study, we measured the serum drug concentration by radioimmunoassay and compared the pharmacokinetic parameters of the 2 schedules. Attempts were made to explain clinical toxicity in terms of pharmacokinetic parameters.

MATERIALS AND METHODS

VDS was supplied by Dr. R. Dyke of the Lilly Laboratories for Clinical Research, Indianapolis, IN, as a lyophilized powder of 10 mg in 10-ml ampuls. The ampuls were refrigerated during storage. Just prior to use, the drug was diluted with bacteriostatic sodium chloride injection solution and then administered either as a slow i.v. bolus (approximately 1 min) through the side arm of a running infusion, or as a 24-hr infusion after further diluting in one liter of 5% dextrose.

Serum VDS levels were measured in a total of 11 patients: 6 after i.v. bolus, 4 after 24-hr infusion, and 1 after bolus and 24-hr infusions given at a 3-week interval. None of the patients had preexisting hepatic or renal impairment, but one (Patient 1) had a moderate third space fluids. All patients had WBC counts more than 4,000 /µl and platelets more than 100,000 /µl. All but one patient (Patient 11) (Table 3) received 4 mg/sq m. One patient (Patient 6) (Table 1) developed transient elevation of transaminases after each of 2 courses of i.v. bolus treatment.

After administration of VDS, either by i.v. bolus or 24-hr infusion, blood samples were collected at selected time intervals (after bolus at 0, 5, 15, and 30 min and then 1, 2, 4, 6, 12, 24, 48, and 72 hr; with the infusion schedule at 0 and 12 hr during infusion and after the infusion at 5 and 30 min and then 1, 2, 4, 8, 24, 48, and 72 hr) from an arm contralateral to the site of the drug administration. Serum was separated from coagulated blood samples by centrifugation and stored at -75° until assay. Informed consent was obtained from each patient prior to the study.

VDS serum levels were measured by radioimmunoassay (12, 13, 16, 17). The reaction tubes (12- x 75-mm polystyrene tubes No. 2054; Falcon Plasticos, Oxnard, CA) consisted of 200 /µl of 0.2 M glycine buffer, pH 8.8, which contained 0.25% human serum albumin (Plasmabase, Cutter Laboratories, Berkeley, CA), 1.0% normal sheep serum (Antibodies, Davis, CA), and 0.0242% m-chloroacetamide; 100 /µl standard or unknown serum (appropriately diluted with the glycine buffer, if necessary), 100 /µl [3H]VDS solution (Amersham/Searle Corp., Arlington Heights, IL; 0.27 Ci or 0.89 ng/tube diluted with 0.02 M acetate buffer, pH 4.4) and 100 /µl rabbit anti-VLB antiserum (Lot No. 24-245-2-G, Eli Lilly Research Laboratories, Indianapolis, IN, diluted 1:2500 with glycine buffer). The contents of the tubes were mixed gently, and the tubes were capped tightly and incubated for 4 days at 4°. At the end of the incubation period, 500 /µl of dextran-coated charcoal suspension (1% Norit-A (Sigma Chemical, St. Louis, MO) and 0.5% dextran 70 (Pharmacia, Uppsala, Sweden)) in glycine buffer were added to each tube, and incubation was continued at room temperature for 30 min with gentle shaking twice. The tubes were centrifuged at 1000 x g for 10 min, and the supernatant was decanted directly into scintillation vials. One-half ml of NCS (Amersham) was added and heated at 50° for 20 min. The material was cooled to room temperature. Ten ml of PCS (Amersham) was added, and the vials were then counted in a liquid scintillation counter (Model LS-355, Beckman Instruments, Palo Alto, CA). Standard solutions were made by diluting VDS in acetate buffer with concentrations ranging from 0.2 to 100 /µg/ml. Control tubes included those containing glycine buffer and [3H]VDS only ("total"). 100 /µl of nonimmune rabbit serum substituted for the antiserum ("blank") and 100 /µl of glycine buffer in place of the standard or unknown ("bound"). The "blank" cpm were subtracted from those of the "bound" to give the actual bound radioactivity, B. The "total"
for the standard and unknown was calculated as:

$$\frac{B}{F} = \frac{\text{Sample cpm} - \text{“blank” cpm}}{\text{“Total” cpm} - \text{sample cpm}}$$

(A)

$B/F$ for the standard curve was plotted on a logit-log scale, and unknown concentrations were calculated based on $t = 1.0$. $B/F$ for the standard and unknown was calculated as:

$$\frac{B}{F} = \frac{\text{Sample cpm} - \text{“blank” cpm}}{\text{“Total” cpm} - \text{sample cpm}}$$

(B)

The VDS standard curve is shown in Chart 2. On the logit-log scale, radioimmunoassay values of VDS were linear in the range of 1.0 to 100 µg/liter. VDS is stable in 0.9% sodium chloride or 5% dextrose for more than 24 hr at room temperature. The drug was also stable in frozen serum when repeatedly defrosted and measured 2 to 3 times during a 6-month time span.

Serum VDS levels after i.v. bolus followed triexponential decay, as confirmed by the precise curve-fit of equation B:

$$c_x(t) = P e^{-\alpha t} + A e^{-\beta t} + B e^{-\gamma t}$$

where $c_x(t)$ is the serum VDS concentration at time $t$ after bolus drug administration; $P$, $A$, and $B$ are constants representing intercepts on the ordinate at time zero; and $\alpha$, $\beta$, and $\gamma$ are the first-order disposition rate constants with $\gamma > \alpha > \beta > 0$. Pharmacokinetic parameters obtained from a single i.v. bolus administration in 7 patients are shown in Tables 1 and 2. An example of the least-squares curve-fit of Equation B to the data is illustrated in Chart 3. From these data, the initial half-life of serum drug decay was approximately 9 min. The second serum half-life was approximately 4 hr, and the third half-life was approximately 35 hr. Patient 6 had pharmacokinetic parameters essentially within the range of experimental variability, except $\beta$ of 0.0085 or the third half-life of approximately 80 hr. The volume of distribution of the central compartment (Chart 1, Compartment 1) was calculated to be approximately 18 liters. VDS showed a high value for exit rate constants ($k_{12}$ and $k_{33}$) from the central compartment, while the elimination rate constant was quite low. This implied that tissue distribution or inactivation rather than elimination was primarily responsible for the drug clearance from the serum.

In contrast to i.v. bolus, the serum drug levels after 24-hr infusion followed biexponential decay, as shown in Chart 4. Least-squares regression fits precisely Equation C:

$$c_x(t) = A' e^{-\alpha' t} + B' e^{-\beta' t}$$

(C)

where $c_x(t)$ is the serum VDS concentration after 24-hr infusion, $T$ is the infusion time (24 hr), and $t$ is the time after the start of infusion. $A'$ and $B'$ are constants representing $y$-axis values at $t = T$, and $\alpha'$ and $\beta'$ are the first-order disposition rate constants with $\alpha' > \beta' > 0$. Pharmacokinetic parameters obtained after 24-hr infusion in 5 patients are shown in Table 3. Comparison of pharmacokinetic parameters in Tables 1 and 3 shows that the peak serum VDS concentration after the 24-hr infusion was approximately 6% of the peak concentration obtained by i.v. bolus. Noting that $\alpha$ and $\alpha'$ as well as $\beta$ and $\beta'$ are equivalent within the range of experimental variability, it is observed that, after a 24-hr infusion of VDS, the $\pi$ phase of the serum is not seen.

For the determination of $c_x(t)$, there were insufficient data points to allow curve-fitting during the infusion period. However, the VDS serum level at the 12th hr after the start of the infusion was 88% of the value within 15 min after the end of infusion in 4 patients. Using this observation plus the shape of the decay curve, with the absence of the $\pi$ phase, an overall serum VDS curve may be estimated which can then be used to approximate $c_x(t)$. Theoretically (20), for an infusion of length $T$, the serum concentration $c_x(t)$ for $t > T$ is given by:

$$c_x(t) = P(T) e^{-\alpha t} + A(T) e^{-\beta t} + B(T) e^{-\gamma t}$$

(D)
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where \( P(T) \), \( A(T) \), and \( B(T) \) are pharmacokinetic *constants* which are functions of the infusion time \( T \):

\[
P(T) = \frac{k_0}{V_i} \left\{ \frac{(E_2 - \beta)(k_{21} - \beta)(\alpha - \beta)(\beta - \gamma)}{\beta^2(\alpha - \beta)(\beta - \gamma)} \right\}
\]

\( (E) \)

\[
A(T) = \frac{k_0}{V_i} \left\{ \frac{(E_2 - \alpha)(k_{21} - \alpha)(\alpha - \beta)(\beta - \gamma)}{\beta^2(\alpha - \beta)(\beta - \gamma)} \right\}
\]

\( (F) \)

\[
B(T) = \frac{k_0}{V_i} \left\{ \frac{(E_2 - \beta)(k_{21} - \beta)(\alpha - \beta)(\beta - \gamma)}{\beta^2(\alpha - \beta)(\beta - \gamma)} \right\}
\]

\( (G) \)

The pharmacokinetic values \( k_{20}, k_{21}, k_{31}, \pi, \alpha, \) and \( \beta \) from Tables 1 and 2 were calculated, not from the "true" bolus administration but, rather, from a \( T = 1/60 \) infusion. Therefore, it is preferred to calculate \( P(T), A(T), \) and \( B(T) \) for all \( T > 1/60 \) hr from \( P, A, \) and \( B \) as follows:

\[
P(T) = P \times \left( \frac{|P(T)|}{P(1/60)} \right) = \frac{101.6}{T} (1 - e^{-4.429}) \quad (H)
\]

\[
A(T) = A \times \left( \frac{|A(T)|}{A(1/60)} \right) = \frac{559.1}{T} (1 - e^{-0.175}) \quad (I)
\]

\[
B(T) = B \times \left( \frac{|B(T)|}{B(1/60)} \right) = \frac{422.2}{T} (1 - e^{-0.0198}) \quad (J)
\]

The values of \( P(24), A(24), \) and \( B(24), \) calculated directly from Equations \( H, I, \) and \( J, \) were 4.23, 22.9, and 6.68, respectively. Of note is the observation that the value of \( P(24) = 4.23 \) is sufficiently small, and the decay \( e^{-\gamma r} \) sufficiently rapid, so as to reduce the impact of the \( \pi \) phase on the serum concentration of VDS after termination of the infusion. It is also of confirmatory importance that calculated \( A(24) = 22.9 \) and \( B(24) = 6.68 \) are close and proportional to the measured values \( A' = 26.4 \pm 3.32 \) and \( B' = 7.5 \pm 1.06 \) from the infusion \( (T = 24) \) data (from Equation C) as summarized in Table 3. The measured values are probably higher than the estimates by virtue of the incorporation of the "hidden" \( P(24) \). In this regard, the calculated value of \( c_\psi(24) \) or \( P(24) + A(24) + B(24) = 33.8 \) corresponds nicely with the measured value of 33.9 (Table 3, \( c_\psi(1) = T \)).

At time \( T, \) by reference to Equation D, the heights of components \( \pi, \alpha, \) and \( \beta \) are given by \( P(T), A(T), \) and \( B(T), \) respectively. Thus, at time \( 1/60 \leq t < T \) during an infusion of length \( T, \) the serum concentration should equal \( P(t) + A(t) + B(t), \) where these values are calculated from Equations \( K, L, \) and \( M, \) below, which are modifications of Equations \( H, I, \) and \( J. \)

\[
P(t) = \frac{101.6}{T} (1 - e^{-4.429}) \quad (K)
\]

\[
A(t) = \frac{559.1}{T} (1 - e^{-0.175}) \quad (L)
\]

\[
B(t) = \frac{422.2}{T} (1 - e^{-0.0198}) \quad (M)
\]

These equations are valid because the total dose administered by time \( t \) is \( \frac{Dose \cdot t}{T} \) so that

\[
k_0 = \frac{Dose \cdot t}{T} = \frac{Dose}{T}
\]
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Table 2
First-order mass transfer rate constant (see Chart 1) to fit serum vindesine levels after i.v. bolus

<table>
<thead>
<tr>
<th>Patient</th>
<th>$k_{12}$ (hr$^{-1}$)</th>
<th>$k_{21}$ (hr$^{-1}$)</th>
<th>$k_{32}$ (hr$^{-1}$)</th>
<th>$k_{23}$ (hr$^{-1}$)</th>
<th>$k_{31}$ (hr$^{-1}$)</th>
<th>Clearance (liters/hr/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.601</td>
<td>0.941</td>
<td>0.397</td>
<td>0.0258</td>
<td>0.224</td>
<td>0.120</td>
</tr>
<tr>
<td>2</td>
<td>6.76</td>
<td>1.31</td>
<td>0.0626</td>
<td>0.0377</td>
<td>0.023</td>
<td>0.279</td>
</tr>
<tr>
<td>3</td>
<td>1.45</td>
<td>0.321</td>
<td>0.272</td>
<td>0.0247</td>
<td>0.122</td>
<td>0.098</td>
</tr>
<tr>
<td>4</td>
<td>1.54</td>
<td>0.235</td>
<td>0.157</td>
<td>0.0234</td>
<td>0.260</td>
<td>0.0617</td>
</tr>
<tr>
<td>5</td>
<td>3.64</td>
<td>1.62</td>
<td>0.141</td>
<td>0.0135</td>
<td>0.092</td>
<td>0.128</td>
</tr>
<tr>
<td>6</td>
<td>4.05</td>
<td>0.813</td>
<td>0.217</td>
<td>0.0472</td>
<td>0.124</td>
<td>0.0449</td>
</tr>
<tr>
<td>7</td>
<td>4.92</td>
<td>1.01</td>
<td>0.319</td>
<td>0.0472</td>
<td>0.124</td>
<td>0.0449</td>
</tr>
</tbody>
</table>

Mean: $3.28 \pm 0.83$, $0.799 \pm 0.174$, $0.359 \pm 0.161$, $0.0336 \pm 0.00513$, $0.154 \pm 0.0255$, $0.132 \pm 0.03$

*Mean ± S.E.

This concept allows for the simulation of the serum concentration both during the infusion and after $t = T$.

$$c_{w}(t) = \begin{cases} \frac{P(t) + A(t) + B(t)}{} & \text{if } \frac{1}{T} \leq t < T, \\ \text{Otherwise, } P(T)e^{-\frac{t}{\text{hr}}} - \eta + A(T)e^{-\frac{t}{\text{hr}}} - \eta + B(T)e^{-\frac{t}{\text{hr}}} - \eta. & \end{cases} \quad (N)$$

Simulations of Equation N are illustrated in Charts 5 and 6 for $T = \frac{1}{T}$ and 24 hr, respectively. Confirming the validity of this model is the calculation that the ratio $c_{w}(12)/c_{w}(t)$ varies between 0.84 and 0.95 for values of $t$ between 0 and 15 min after the end of the infusion at $T = 24$. This corresponds with the measured value of 0.88.

The $c 	imes t$ for the infusion data can now be estimated by integrating Equation N (see "Appendix"). This has been performed for the mean infusion data (see Table 3, footnotes) and the bolus data (see Table 1, footnotes). It is to be noted that the $c 	imes t$ for the 24-hr infusion was identical to that for bolus administration.

DISCUSSION

The radioimmunoassay used in the present study is a sensitive one, but it also cross-reacts with other Vinca alkaloids (12, 16). This implies that the method might cross-react not only with the parent VDS but probably with some metabolite(s) present in the biological material. In this context, what we expressed as VDS should more accurately be called VDS equivalents. We have used the term VDS in this treatise in order to avoid confusion when one compares the data produced from different institutions; most of the earlier Vinca alkaloid pharmacology data using radioimmunoassay were derived by the use of a method developed by Root et al. (17).

Nelson et al. (12, 13) and Owellen et al. (16) reported pharmacokinetic parameters of VDS in humans obtained by similar radioimmunoassay. They have shown that the central compartment was compatible with the total blood volume. In contrast, the central compartment obtained in this report is approximately 4-fold greater. The reason for this discrepancy is unclear. In order to avoid extravasation of the drug, we administered it in a slow i.v. bolus (over approximately 1 min) through the side arm of running infusion. This might have caused a low $P + A + B$ value (by Equations K, L, and M) and, consequently, a high $V_1$. On the other hand, we noticed that our $V_1$ value for VDS is similar to the reported $V_1$ for VCR (12) and VLB (12, 15). Our $V_2$ and $V_3$ values are in accord with those reported by Owellen et al. (16). The mean terminal serum half-lives in our study are greater than the reported values (12, 16) but clearly less than...
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Table 3
Pharmacokinetic parameters obtained from a 24-hr infusion of vindesine

Biexponential serum decay curve followed Equation C.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Patient</th>
<th>A' (µg/liter)</th>
<th>α' (hr⁻¹)</th>
<th>B' (µg/liter)</th>
<th>β' (hr⁻¹)</th>
<th>(c_0(t = T)) (µg/hr/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>4.0</td>
<td>7.2</td>
<td>19.2</td>
<td>0.268</td>
<td>5.85</td>
<td>0.0201</td>
</tr>
<tr>
<td>8</td>
<td>4.0</td>
<td>6.0</td>
<td>35.0</td>
<td>0.163</td>
<td>8.33</td>
<td>0.0245</td>
</tr>
<tr>
<td>9</td>
<td>4.0</td>
<td>6.0</td>
<td>24.0</td>
<td>0.182</td>
<td>5.69</td>
<td>0.00342</td>
</tr>
<tr>
<td>10</td>
<td>4.0</td>
<td>8.4</td>
<td>27.4</td>
<td>0.157</td>
<td>10.1</td>
<td>0.01937</td>
</tr>
<tr>
<td>11</td>
<td>5.0</td>
<td>9.0</td>
<td>18.6</td>
<td>0.242</td>
<td>4.14</td>
<td>0.00616</td>
</tr>
<tr>
<td>Mean</td>
<td>26.4 ± 3.32a-c</td>
<td>0.202 ± 0.025</td>
<td>7.50 ± 1.06b</td>
<td>0.0147 ± 0.00417</td>
<td>33.9 ± 4.06c</td>
<td></td>
</tr>
</tbody>
</table>

* Patient 7 in Table 1 was also studied for 24-hr infusion.
* Mean ± S.E.
* Data from Patient 11, who received a different dose from the others, were not used for calculation.
* The \(c \times t\), estimated by integration of Equation N (see "Appendix"), is 1083 (µg/hr/liter).

those reported for VCR. The discrepancy of the half-life obtained from this study and the earlier report is not clear. Our data are partially influenced by a value in Patient 6, who had a terminal half-life of 80 hr.

The reasons why Patient 6 had a prolonged terminal half-life are unclear. The only difference in clinical course of this patient from the others is the transient elevation of transaminases after each course of VDS administration. He might have had preexisting subclinical hepatic impairment. The dose we used (4 mg/sq m) is larger than those reported by Nelson et al. (13); thus, this could possibly be a dose-dependent phenomenon. Owellen et al. used the doses ranging from 1.5 to 4.0 mg/sq m (16), but the number of patients in each dose level is too small to conclude the dose dependence. All the patients we studied had platelets more than 100,000/µl, whereas the reported study did not mention the platelet value. A possibility of platelet binding as a factor influencing the half-life could not be excluded.

Somewhat wide fluctuations of pharmacokinetic parameters from one patient to the other were noted for both bolus and 24-hr infusion. We noted that the \(P\) value of Patient 1 is smaller than are the \(P\) values of the other patients. This patient had a large retroperitoneal sarcoma and a moderate amount of leg edema.

The small \(P\) value may be related to this. The low \(P\) value did not influence the \(c \times t\) value, however. Determinants for pharmacokinetic parameters for VDS of possible importance include tumor load and carrier protein concentration (5); these and other such factors as nutritional status and concurrent medications might have affected the pharmacokinetic parameters.

Pharmacokinetic parameters from postinfusional blood curves have been assessed for other drugs (8). Although a mathematical equation which enables one to determine the parameters identical to an i.v. bolus by utilizing the postinfusion curve has been presented (8), the present study clearly indicates the limitation of such an approach because of the likelihood that, after a prolonged infusion, distribution phase constants \(P\) and \(B\) may not be recognizable from experimental data.

Increased toxicity in patients with major hepatic impairment (14) and increased terminal half-life in Patient 6 suggested that the liver plays a major role in VDS excretion or metabolism. Determination of the influence of preexisting hepatic dysfunction on serum VDS pharmacokinetics would be of interest. Neuronal toxicity was more insidious and difficult to quantify. Obviously, pharmacokinetic parameters obtained after the first course of chemotherapy are inadequate to explain the delayed
neurological toxicities.

We noted that the comparison of the 2 schedules is a practical method to correlate the relationship between pharmacokinetic data and clinical toxicity. Thus, our pharmacokinetic evaluation revealed that the 24-hr infusion of VDS produced only one-sixteenth of the peak serum level achieved by i.v. bolus, whereas the c x t value after 24-hr infusion was identical to that after i.v. bolus. Since the observed hematological toxicities were essentially similar for the 2 schedules (14), it may be concluded that the toxicity is less related to the peak serum levels than that immunocassayable c x t and/or the elimination half-life.

The observation that the c x t for the bolus administration is identical to that after 24-hr infusion should be of interest. This was mathematically confirmed. Theoretically, c x t would be constant, regardless of infusion time. One might be tempted to conclude that the toxicity is less related to the peak serum levels than that immunocassayable c x t and/or the elimination half-life.

Implications of these observations on the therapeutic effects remain to be elucidated. In our Phase I study, none of the patients went into partial or complete responses (14). It is noteworthy that remissions were reported to be induced in patients with acute leukemia with a 48-hr infusion, whereas a twice-daily i.v. bolus regimen did not produce a response (10). Similarly, continuous infusion of VDS for 5 days appeared to be more efficacious than the bolus schedule in the treatment of patients with refractory breast carcinoma (21). The improved therapeutic efficacy of VDS infusion over bolus cannot be explained from available pharmacokinetic parameters alone. In this context, the following considerations may be offered. First, it is possible that pharmacokinetic parameters (c x t, half-lives, etc.) from 48-hr infusion or 5-day continuous infusion are entirely different from those of 24-hr infusion. This possibility is, however, unlikely because c x t appears constant regardless of infusion time. Second, therapeutic efficacy may be related to a biological concentration-effect window (biologically effective drug concentration x exposure time) rather than mere c x i. Third, N-desformyl-VCR, an inactive metabolite, was identified in the urine of a patient receiving VCR (18). It is possible that such a metabolite may be present in radioimmunoassayable VDS, and intracellular metabolism of VDS may be independent of serum c x t. In-depth pharmacokinetic studies of VDS for both bolus and infusion in patients with VDS-sensitive tumors might give insight into the relationship between pharmacokinetic parameters and therapeutic efficacy.

Acknowledgments

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References

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