Pharmacokinetics and Pharmacodynamics of 9-Aminocamptothecin Infused Over 72 Hours in Phase II Studies

Hironobu Minami, Thomas E. Lad, M. Kelly Nicholas, Everett E. Vokes, and Mark J. Ratain


ABSTRACT

A novel derivative of camptothecin, 9-aminocamptothecin (9-AC), is currently under Phase II evaluation in various cancers. Exceptionally mild toxicities were observed in patients with brain tumors who were treated with anticonvulsants. To investigate a pharmacokinetic interaction between 9-AC and anticonvulsants, and to evaluate the pharmacodynamics of 9-AC, we investigated the clinical pharmacology of 9-AC, administered by a 72-h infusion, in three Phase II studies. Plasma concentrations of total 9-AC (lactone plus carboxylate) at a steady state were measured in 56, 10, and 14 patients with non-small cell lung cancer, malignant glioma, and head and neck cancer, respectively. For lung cancer or glioma patients, 9-AC was infused at 45 (51 patients) or 59 (15 patients) µg/m²/h, and 9-AC was infused at 35.4 µg/m²/h in head and neck cancer patients. All glioma patients had been treated with phenytoin or carbamazepine. 9-AC clearance did not differ among the dosage rates, but differed according to the diseases (P = 0.002). Glioma patients had a higher clearance (1.0 – 18.0; median, 2.0 liters/h/m²) than lung cancer patients (0.3–5.1; median, 0.9 liters/h/m²). A logistic regression model described the relationship between the 9-AC concentration and the probability of grade 4 neutropenia, which was the main toxicity. Observed incidences of grade 4 neutropenia for patients with model-predicted probability of 0–20%, 20–40%, and 40–100% were 10%, 32%, and 67%, respectively, and corresponded to 9-AC concentration of <54, 54–86, and >86 ng/ml, respectively. Anticonvulsants seem to induce the clearance of 9-AC, and the concentration of 9-AC predicts the probability of grade 4 neutropenia.

INTRODUCTION

A novel derivative of camptothecin, 9-AC, shows antitumor activity by inhibiting topoisomerase I. In preclinical experiments, 9-AC showed activity against various tumors (including those of the breast, colon, lung, and prostate) and melanoma (1–5) and is currently under clinical Phase II evaluation. Like other camptothecin derivatives, a closed lactone ring of 9-AC undergoes pH-dependent hydrolysis to yield an open carboxylate-form, which predominates over the lactone in human plasma at equilibrium (6). An intact lactone ring is necessary for topoisomerase I inhibition (7).

In preclinical experiments, greater antitumor activity was suggested with prolonged maintenance of lower concentrations of 9-AC (8), and Phase I studies were conducted in humans using 72-h continuous infusion (9, 10). The dose-limiting toxicities were neutropenia and thrombocytopenia. The recommended doses for Phase II studies supported by filgrastim (G-CSF) were 47 µg/m²/h every 2 weeks for heavily pretreated patients or patients who had received prior pelvic irradiation and 59 µg/m²/h every 2 weeks for minimally pretreated patients (9). However, after febrile neutropenia and grade 4 thrombocytopenia were consistently observed in patients treated with 59 µg/m²/h of 9-AC and with G-CSF in a number of Phase II studies, the recommended dose was subsequently reduced to 45 µg/m²/h for 72 h every 2 weeks (9). The recommended dose without G-CSF was 35 µg/m²/h for 72 h every 2 weeks (9). However, in a Phase II study of 9-AC at this dose for recurrent high-grade astrocytomas, no grade 3 or greater myelosuppression was noted in 29 patients who had been treated with anticonvulsants, and a further dose-escalation study was restarted in patients treated with anticonvulsants (11). Anticonvulsants are known to induce enzymes that metabolize various drugs (12–14), and it is important to evaluate whether patients taking anticonvulsants have greater clearance of 9-AC than those without anticonvulsant therapy.

Multi-institutional Phase II studies were conducted at our institutions for NSCLC (15), malignant gliomas, and squamous carcinomas of the head and neck (16). We evaluated the pharmacokinetics and pharmacodynamics of 9-AC in patients treated in these Phase II studies to confirm that anticonvulsants...

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increase 9-AC clearance and to investigate the relationship between 9-AC pharmacokinetics and toxicities.

**PATIENTS AND METHODS**

**Patients and Treatment.** Data used in this study were obtained as part of Phase II studies of 9-AC in patients with NSCLC (15), malignant glioma, and squamous cell carcinoma of the head and neck (16). Excluded from the study were patients with lung cancer who had prior chemotherapy, but entry was not denied those with glioma or head and neck cancer who had prior chemotherapy. Of 58 patients with NSCLC, 57 had blood sampling for the measurement of 9-AC concentrations. One patient with brain metastases, in whom the use of anticonvulsants was not confirmed, was excluded from analysis because an important objective was to evaluate the effect of anticonvulsants on the pharmacokinetics of 9-AC. Ten of 14 patients with glioma and all 14 patients with head and neck cancer had blood sampling for pharmacokinetics. Data from these 80 patients were used in this study (Table 1). Protocols of these Phase II studies were approved by local Institutional Review Boards, and all patients gave written informed consent.

9-AC formulated in dimethylacetamide was diluted in polyethylene glycol 400 and phosphoric acid and infused over 72 h every 2 weeks. Initially, 13 patients with NSCLC and 2 patients with glioma were treated with 9-AC at a rate of 59 \( \mu \text{g/m}^2/\text{h} \), which was decreased to 45 \( \mu \text{g/m}^2/\text{h} \) for subsequent patients with NSCLC \((n = 43)\) or glioma \((n = 8)\). From day 5, G-CSF at a dose of 5 \( \mu \text{g/kg/day} \) was given s.c. to all patients with NSCLC or glioma until the recovery of the neutrophil count. Patients with head and neck cancer were treated with 9-AC at a rate of 35.4 \( \mu \text{g/m}^2/\text{h} \) for 72 h without G-CSF every 2 weeks. Details of these studies will be published elsewhere (15, 16).

**Pharmacokinetics.** Heparinized blood was drawn for the measurement of 9-AC concentrations at 23, 47, and 71 h into the infusion of the first cycle. Plasma was separated immediately and frozen at \(-70^\circ\text{C}\) until analysis. Frozen plasma samples from each institution were shipped to the University of Chicago, where the concentration of total (lactone plus carboxylate) 9-AC was measured.

Quantitation of 9-AC was performed using a previously reported high-performance liquid chromatography method (17), with minor modification. Briefly, 150 \( \mu \text{l} \) of plasma was acidified with 15 \( \mu \text{l} \) of 1.5 M perchloric acid, and the mixture was vortexed. Acidified methanol \( (450 \mu\text{l}) \) and the internal standard (camptothecin) were added, and the sample was centrifuged. Supernatant \( (200 \mu\text{l}) \) was mixed with an equal volume of 25 mM KH\(_2\)PO\(_4\) (pH 3.0), and 200 \( \mu\text{l} \) of the sample was injected into the high-performance liquid chromatography system. Chromatography was performed with an isocratic mobile phase of 25 mM KH\(_2\)PO\(_4\):acetonitrile:methanol \((74:16:10, \text{v/v/v}; \text{pH} 3.5)\) at a flow rate of 1 ml/min on 3.9 \( \times \) 150 mm Nova-Pak C\(_{18}\).

Postcolumn acidification was achieved with 2% phosphoric acid mixed in line with the column effluent at a rate of 0.2 ml/min, which brought the pH of the mixture to 2.0. The drug was detected using a fluorescence detector at an excitation wavelength of 365 nm and emission wavelength of 455 nm. The LOQ was 5 ng/ml, and intraday and interday assay variability was \(<5\%\), except for near the LOQ where intraday and interday variability was 6% and 12%, respectively.

A median of the three measured concentrations was used as

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Lung cancer</th>
<th>Glioma</th>
<th>Head and neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>36–82</td>
<td>25–71</td>
<td>34–73</td>
</tr>
<tr>
<td>Median</td>
<td>64</td>
<td>52</td>
<td>63</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td></td>
<td>7/3</td>
<td>13/1</td>
</tr>
<tr>
<td>PS(^a) (0/1/2)</td>
<td>17/28/11</td>
<td>0/64</td>
<td>6/5/3</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>4.9–8.6</td>
<td>6.1–8.3</td>
<td>6.4–8.2</td>
</tr>
<tr>
<td>Median</td>
<td>7.0</td>
<td>6.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>2.5–5.2</td>
<td>3.5–5.5</td>
<td>3.5–4.5</td>
</tr>
<tr>
<td>Median</td>
<td>3.8</td>
<td>4.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.1–1.0</td>
<td>0.1–0.8</td>
<td>0.3–1.3</td>
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<tr>
<td>Median</td>
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<td>0.4</td>
<td>0.5</td>
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<tr>
<td>Creatinine (mg/dl)</td>
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<td></td>
<td></td>
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<td>Range</td>
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<td>0.6–1.3</td>
<td>0.6–1.3</td>
</tr>
<tr>
<td>Median</td>
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<td>0.9</td>
<td>1.0</td>
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<tr>
<td>BUN (mg/dl)</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>6–27</td>
<td>6–26</td>
<td>7–25</td>
</tr>
<tr>
<td>Median</td>
<td>13</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Previous chemotherapy (yes/no)</td>
<td>0/56</td>
<td>4/6</td>
<td>5/9</td>
</tr>
<tr>
<td>Previous radiotherapy (yes/no)</td>
<td>15/41</td>
<td>10/0</td>
<td>12/2</td>
</tr>
<tr>
<td>Dose ((\mu\text{g/m}^2/\text{h}))</td>
<td>45 (45(^b)) or 59 (13(^b))</td>
<td>45 (8(^b)) or 59 (2(^b))</td>
<td>35.4</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

\(^a\) PS, performance status; BUN, blood urea nitrogen.

\(^b\) Number of patients.
a representative concentration for each patient. When the median concentration in a patient was below the LOQ (5 ng/ml), half of the LOQ (2.5 ng/ml) was used as an estimate of the concentration. The total clearance of 9-AC was calculated by dividing the dose rate by the concentration. The Kruskal-Wallis test was used to compare the 9-AC clearance among three groups designated according to dosage rates or diseases, respectively; the Mann-Whitney U test was used to compare every combination of two groups of the disease where the adjusted P of 0.0167 (=0.05/3) was considered to be significant. Otherwise, a P of 0.05 was the cutoff of significance for two-way comparison by the Mann-Whitney U test.

**Pharmacodynamics.** Data from six (four lung cancer and two glioma) patients whose blood cell counts were not checked more than once before the second cycle were excluded from pharmacodynamic analysis; therefore, data (first cycle only) of the remaining 74 patients were used. The pharmacodynamic relationship was examined by plotting the surviving fraction of the absolute neutrophil count or the platelet count versus the 9-AC concentration. The surviving fraction (%) of the blood cell count was defined as 100 × (nadir count)/(pretreatment count). These relationships were fitted to a sigmoid Emax model: surviving fraction = Emax × [1- C/(EC_{50} + C)], where Emax was the maximum change, C was the 9-AC concentration, r was the sigmoidicity factor that defines the steepness of the response curve, and EC_{50} was the concentration value that gives 50% of the maximal effect (Emax). These parameters were estimated by the nonlinear least-squares regression program WinNonlin (Scientific Consulting, Inc., Apex, NC).

Neutropenia was the main toxicity, and a logistic regression model was used to predict the probability of grade 4 neutropenia with 9-AC concentrations. The patient characteristics listed in Table 1, the use of G-CSF, 9-AC concentrations, and pretreatment neutrophil counts were tested as possible covariates in a logistic regression model. All statistical analyses were performed using the program Number Cruncher Statistical Systems (NCSS, Kaysville, UT).

**RESULTS**

Pharmacokinetics and pharmacodynamics of 9-AC were evaluated in 56 patients with NSCLC, 10 patients with malignant gliomas, and 14 patients with squamous cell carcinoma of the head and neck (Table 1). All 10 patients with glioma had been treated with anticonvulsants: 4 patients with phenytoin and 6 patients with carbamazepine. No patients with lung or head and neck cancer had been treated with anticonvulsants. The distribution of previous treatments differed among studies, depending on the protocols, but other eligibility criteria for the three studies were similar (Table 1). Among 80 patients, concentrations at 23, 47, and 71 h were measured in 78, 76, and 75 patients, respectively. Plasma concentrations of 9-AC at each sampling point were distributed widely, and median concentrations at 23, 47, and 71 h of all patients were 33.7, 38.6, and 44.9 ng/ml, respectively (Fig. 1). Although concentrations at 23 h were significantly lower than those at 47 h (P = 0.003) or 71 h (P = 0.004) by pair-wise comparison using the Wilcoxon signed-rank test, there was moderate intrapatient variability with coefficient of variations ranging from 1–173% (median, 24%). When the median value of three concentrations in each patient were compared with the median of two concentrations at 47 and 71 h, no difference was observed (40.0 versus 40.7 ng/ml). Therefore, the median value of 23, 47 and 71-h concentrations was used for further analysis as a representative concentration for each patient.

Marked interpatient variability in 9-AC concentrations and hematological toxicities was observed (Table 2). When the clearance of 9-AC by either dose rates or diseases was compared, no significant difference was observed among the different dosages. However, clearance significantly differed among the diseases (P = 0.002), and clearance in patients with lung cancer and that of patients with glioma was significantly different (P = 0.01; Table 3). To confirm the difference of 9-AC clearance in patients with and without anticonvulsant treatments, we compared the clearance of glioma patients with that of lung cancer patients who were treated at the same dose rate of 45 μg/m²/h. The 9-AC clearance of patients with glioma (n = 8) was significantly (P = 0.01) higher than that of patients

![Fig. 1 Distributions of total 9-AC concentrations at 23, 47, and 71 h during a 72-h continuous infusion of 9-AC. Median concentrations of lung cancer patients (solid line) and of glioma patients (dashed line) treated at the same dose rate, 45 μg/h/m², are shown.](image-url)
Pharmacology of 9-Aminocamptothecin

with lung cancer \( (n = 43) \). The clearance of 9-AC in glioma patients treated with carbamazepine (range, 1.0–18.0 liters/h/m\(^2\); median, 2.0 liters/h/m\(^2\)) was not different from that in patients treated with phenytoin (range, 1.0–8.2 liters/h/m\(^2\); median, 2.0 liters/h/m\(^2\)).

The main toxicity was neutropenia and leukopenia, and some patients experienced thrombocytopenia. In accordance with the higher clearance of 9-AC in patients with glioma than patients with lung cancer, surviving fractions of leukocytes in glioma patients treated with 45 g/m\(^2\)/h (median, 94%; range, 43–141%) was significantly \( (P = 0.03) \) higher than those of lung cancer patients treated at the same dose rate (median, 55%; range, 1–120%). There was a borderline significant \( (P = 0.09) \) difference in surviving fractions of neutrophils between patients with glioma (median, 93%; range, 16–142%) and lung cancer (median, 50%; range, 0–164%). The same tendency was observed for thrombocytopenia (median, 71% versus 39%; range, 32–196% versus 1–113%; \( P = 0.25 \)).

Surviving fractions of neutrophils or platelets were plotted against 9-AC concentrations (Figs. 2 and 3). Patients with head and neck cancer did not receive G-CSF while patients with lung cancer or glioma (Fig. 2). These relationships were described using inhibitory sigmoid Emax models as

\[
\text{Surviving fraction of neutrophil} = 103 \times \left[ 1 - \frac{C^{1.3}}{C^{1.3} + 56^{1.3}} \right] \\
\text{Surviving fraction of platelet} = 81 \times \left[ 1 - \frac{C^{2.5}}{C^{2.5} + 87^{2.5}} \right]
\]

but the correlations were only modest \((r = 0.4; P < 0.001)\).

Grade 4 neutropenia was observed in 14 lung cancer patients and 1 glioma patient. When a logistic regression model was used to predict the probability of grade 4 neutropenia, only the 9-AC concentration was selected as a significant variable \((P = 0.003)\). Other variables, including G-CSF, age, and previous radiotherapy or chemotherapy were not incorporated into the model as a significant covariate. Therefore, we selected the one-parameter logistic regression model with the 9-AC concentration: \( P = 1/(1 + e^{3.06 - 0.031C}) \) where C denoted concentration. To evaluate the predictability for grade 4 neutropenia with the logistic regression model, patients were divided arbitrarily into subgroups with a sufficient number of patients depending on the model-predicted probability of grade 4 neutropenia of 0–20%, 20–40%, 40–100%, and the model-predicted probabilities were compared with the actual rates of grade 4 neutropenia (Table 4). Corresponding 9-AC concentrations of each subgroup are also listed in Table 4. Predicted probability of grade 4 neutropenia was increased as the concentration of 9-AC was increased, and good agreement between the observed probabilities and the probabilities predicted by the model was observed.

**DISCUSSION**

In this pharmacological analysis of three Phase II studies of 9-AC, patients with glioma who had been treated with the anticonvulsants had a greater clearance and lower concentrations of 9-AC than patients with lung cancer who had not been treated with the anticonvulsants, although they were treated at the same doses of 9-AC (45 or 59 g/m\(^2\)/h for 72 h). Patients with glioma had milder toxicities than lung cancer patients. This result was supported by the observation in another Phase II study of 9-AC for brain tumors that unexpectedly mild toxicities led to termination of that study and initiation of a further escalation study in such patients (11). All of our glioma patients

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**Table 3** 9-AC clearance by dose rate and study

<table>
<thead>
<tr>
<th>Dose rate (g/hr/m(^2))</th>
<th>Lung (liters/h/m(^2))</th>
<th>Glioma (liters/h/m(^2))</th>
<th>Head and neck (liters/h/m(^2))</th>
<th>Total (liters/h/m(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.4</td>
<td>ND*</td>
<td>ND</td>
<td>1.6 (14)</td>
<td>1.6 (14)</td>
</tr>
<tr>
<td>45</td>
<td>0.9 (43)</td>
<td>1.8 (8)</td>
<td>ND</td>
<td>1.0 (51)</td>
</tr>
<tr>
<td>59</td>
<td>1.0 (13)</td>
<td>5.2 (2)</td>
<td>ND</td>
<td>1.0 (15)</td>
</tr>
<tr>
<td>Total</td>
<td>0.9* (56)</td>
<td>2.0* (10)</td>
<td>1.6* (14)</td>
<td></td>
</tr>
</tbody>
</table>

* Range and medians of 9-AC clearance (liters/h/m\(^2\)) are listed. Patient numbers are in parentheses.
  * ND, no data.
  * Significant difference by Kruskal-Wallis test.

**Fig. 2** Relationship between total 9-AC concentrations and the surviving fractions of neutrophils in patients treated with a 72-h continuous infusion of 9-AC.

**Fig. 3** Relationship between total 9-AC concentrations and the surviving fractions of platelets in patients treated with a 72-h continuous infusion of 9-AC.
and most of the patients in the other study (11) had been treated with anticonvulsants, phenytoin, or carbamazepine, which are known to induce enzymes that metabolize a variety of drugs, including cytochrome P450 microsomal enzymes and glucuronosyltransferases (12–14). Although a difference of 9-AC clearance between patients who were and were not receiving enzyme-inducing anticonvulsants was not confirmed in their study (11), our patients with glioma had a higher clearance of 9-AC compared with those not taking the anticonvulsants. Although the exact mechanism of the greater clearance of 9-AC in patients who had been treated with phenytoin or carbamazepine remains to be elucidated, the anticonvulsants might decrease the plasma concentration of 9-AC by inducing 9-AC metabolism. However, there are no known metabolites of 9-AC. The other possible mechanism of the greater clearance might be increased biliary drug excretion in patients treated with anticonvulsants. 9-AC is known to be eliminated in feces (18), and camptothecin derivatives are excreted into bile via members of ATP-binding cassette family of transporters (19). Another camptothecin derivative, CPT-11, and its active metabolite SN-38 are substrates for one of these transporters (MRP 2), and MRP 2 expression is inducible with various drugs, including phenobarbital (20). Expression of another transporter, MRP 3, is also induced with phenobarbital and other drugs (21). Although whether 9-AC is a substrate of these transporters and whether these transporters are induced with carbamazepine and phenytoin are not yet known, it is also possible that anticonvulsants might induce carrier-mediated excretion of 9-AC. We cannot ascertain whether the effect of anticonvulsants is on the clearance of the lactone or carboxylate forms because there are potential differences in their metabolism and excretion.

For pharmacological analysis, we used the median value of concentrations from 23–71 h of infusion, assuming that a steady state was achieved by 23 h. The half-life of the total 9-AC was reported to be 8 h in a Phase 1 study (22), suggesting that 23 h might not be long enough to achieve a steady state. However, the increase in the total 9-AC concentration from 24 h to 72 h seemed to be small (22), and the median values of three concentrations and two concentrations at 47 and 71 h in this study were the same. Therefore, we do not believe that including concentrations at 23 h in our analysis affected the results.

There is a large component of residual variability in the sigmoid Emax model relating the 9-AC concentration and the surviving fraction of neutrophils or platelets (Figs. 2 and 3). The activity of the camptothecins depends on a closed lactone ring (7), which rapidly hydrolyzes in aqueous solution at a physiological pH to generate an inactive ring-opened carboxylate in a reversible and nonenzymatic fashion (6, 23). The equilibrium between lactone and carboxylate depends on pH, and in buffered saline at pH 7.4, 20% of 9-AC exists as a lactone form at equilibrium, which decreases to <0.5% in plasma (6). This was due to higher protein binding of the carboxylate form of 9-AC than the lactone form. Total (lactone plus carboxylate) concentration of 9-AC was measured in our studies while only the closed lactone form is considered pharmacologically active. It is possible that measurement of the lactone form might have allowed determination of a superior model. However, theoretically there should be minimal interpatient variability in the lactone to carboxylate ratio, unless there is considerable interpatient variability in the relative protein binding of the lactone and carboxylate, because this is a reversible pH-dependent reaction. Direct measurements of the free 9-AC concentration would likely yield a superior model; but such studies are extremely difficult technically because of the high degree of protein binding of both the lactone and carboxylate and the potential for interconversion in vitro.

G-CSF was used in the patients with lung cancer or glioma. However, the distribution of these patients and patients with head and neck cancer who did not receive G-CSF were not different on the scatter plots of neutropenia versus 9-AC concentrations, and the use of G-CSF did not contribute to the predictability of grade 4 neutropenia in the logistic regression model. The large interpatient variability of the relationship between neutropenia and total 9-AC concentrations seemed to obscure the effect of G-CSF on the degree of neutropenia.

Using a one-parameter logistic regression model with 9-AC concentration, the probability of grade 4 neutropenia might be predicted, and the model may be useful in the management of patients treated with 9-AC over 72 h, although it should be validated in a separate population of patients.

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REFERENCES


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