Clinical Pharmacokinetics of the Anthrapyrazole CI-941: Factors Compromising the Implementation of a Pharmacokinetically Guided Dose Escalation Scheme

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ABSTRACT

The pharmacokinetics of the anthrapyrazole CI-941 has been investigated in conjunction with the Phase I evaluation of the drug with the intent of applying a pharmacokinetically guided dose escalation strategy. A starting dose of 5 mg/m² was chosen, based on one-tenth the 10% lethal dose in mice. Due to the steep dose lethality relationship and nonlinear pharmacokinetics in mice, a target area under the CI-941 plasma concentration × time curve (AUC) of 110 μM × min (i.e., 40% of the mouse 10% lethal dose AUC) was chosen. This AUC was achieved in mice at 40 mg/m². A total of 37 patients received 74 courses of CI-941 (5 to 55 mg/m²), with 26 patients consenting to pharmacokinetic monitoring. CI-941 was rapidly cleared from plasma, and a triexponential open model could be fitted to the data (t₁/₂ = 7.6 ± 2 min, tₑ = 65 ± 27 min, tₑ = 21 ± 9 h). CI-941 was subjected to only limited urinary excretion, accounting for 5.2 ± 2.8% of the administered dose. Wide interpatient variability in CI-941 clearance and the dose was escalated in 5-mg/m² increments until the maximally tolerated dose was achieved. A number of investigations were performed to study potential reasons for variability in CI-941 clearance. However, CI-941 plasma protein binding (95 ± 1%) and measures of pretreatment renal (Cr-EDTA clearance), hepatic (plasma alanine transaminase and alkaline phosphatase levels), or cardiac function (left ventricular ejection fractions) did not relate strongly to CI-941 clearance. In patients treated at 40 mg/m², the AUC values (156 to 415 μM × min) approximated or exceeded the target AUC. Fifty mg/m² was the Phase II recommended dose. Further prospective studies are warranted to assess the utility of pharmacokinetically guided dose escalation strategies and to determine whether or not the variability encountered in clearance is unique to CI-941.

INTRODUCTION

The Phase I testing of a new anticancer drug is conducted to seek evidence of activity and to qualitatively and quantitatively assess drug toxicity. The latter involves determining a MTD, which is, the highest dose which can be administered which produces tolerable, manageable, and reversible toxicity (1). This objective is based on the premise that the greater the amount of drug that can be given, the more likely will be the chance of therapeutic activity (2-5). Data from Phase I studies are then used to recommend a safe dose for Phase II studies, where evidence of activity against specific disease types is sought.

Generally, for conventional cytotoxic drugs, a dose equivalent to the one-tenth LD₉₀ in the mouse (with respect to surface area) is a safe Phase I starting dose (6). Providing no toxicity is encountered at the starting dose, doses are then escalated using empirical schemes such as the modified Fibonacci series, until the MTD has been achieved. However, a number of problems have become apparent with the use of such empirical schemes. Although, in general, there is a good agreement between the mouse LD₉₀ and the human MTD, sufficient variation exists to preclude the use of large increments throughout dose escalation. Consequently, if the human MTD is substantially greater than the mouse LD₉₀, many dose escalation steps will be required. This can make the conduct of Phase I trials lengthy, waste patient and hospital resources, and result in the treatment of a large number of patients at subtherapeutic doses. Conversely, if the human MTD is less than the mouse LD₉₀, patients run the risk of receiving a toxic dose because initial dose increments are relatively large (7).

The disparity between the mouse LD₉₀ and human MTD (7) may be due to either pharmacokinetic or pharmacodynamic variables (8). Pharmacodynamic variables, such as differences in target cell sensitivity or in the levels of critical macromolecular targets, are likely to contribute to interspecies differences in drug toxicity. In addition to these pharmacodynamic variables, differences in the pharmacokinetics of the drug (namely absorption, distribution, metabolism, and excretion) also influence the exposure of target cells to the active drug.

Collins et al. (7) postulated that the disparity between the LD₉₀ in mice and the MTD in humans may largely be due to pharmacokinetic variables. Accordingly, a new approach to dose escalation which takes into account any species differences in the pharmacokinetics of a drug has been proposed (7). Having calculated a Phase I starting dose by conventional means, namely, the dose equivalent to one tenth the LD₉₀ in mice (in terms of mass/unit surface area) (7), the new component of the strategy is to measure the pharmacokinetics of the drug at the LD₉₀ in mice to determine the AUC at this dose. Retrospective studies have shown that the AUC in mice at the LD₉₀ dose is, for a number of agents, similar to the AUC at the MTD in humans (7-10) and, hence, it can be used as a target AUC for Phase I studies. In brief, a PGDE scheme can be summarized as follows: (a) determine the LD₉₀ in mice; (b) determine drug exposure (AUC) at the LD₉₀; (c) treat patients at one tenth the LD₉₀ in mice (in terms of mass/unit surface area) (7), the new component of the strategy is to measure the pharmacokinetics of the drug at the LD₉₀ in mice to determine the AUC at this dose. Retrospective studies have shown that the AUC in mice at the LD₉₀ dose is, for a number of agents, similar to the AUC at the MTD in humans (7-10) and, hence, it can be used as a target AUC for Phase I studies. In brief, a PGDE scheme can be summarized as follows: (a) determine the LD₉₀ in mice; (b) determine drug exposure (AUC) at the LD₉₀; (c) treat patients at one tenth the LD₉₀ (a predicted safe starting dose); (d) measure patient drug exposure (AUC) at the Phase I starting dose; (e) choose an escalation scheme based on the margin between the observed Phase I starting dose AUC and the target (mouse LD₉₀) AUC; and (f) escalate the dose (in 3 to 4 steps) until the target AUC and/or the MTD has been achieved.

Overall, the application of a PGDE scheme should minimize the number of patients treated at subtherapeutic doses, reduce the total number of escalation steps, and hence save on both patient and hospital resources (7-10).

The anthrapyrazole CI-941 (Fig. 1) is a new synthetic DNA-complexing drug (11, 12) with broad spectrum antitumor activ-
ity, equivalent to that of doxorubicin in experimental tumors (13, 14). In contrast to doxorubicin, which possesses a para-quinone group, CI-941 as a quinonimine is difficult to reduce metabolically to a reactive drug-free radical (15). As a result CI-941 does not give rise to significant amounts of reactive oxygen species or induce lipid peroxidation in vitro (15), factors which have been implicated in the etiology of doxorubicin cardiotoxicity (16). Hence, CI-941 is unlikely to induce cardiotoxicity by a free radical-mediated mechanism (15). On the basis of these preclinical antitumor and biochemical toxicology data, CI-941 was selected for Phase I clinical evaluation.

The anthrapyrazole CI-941 appeared to be a suitable candidate for a PGDE scheme for the following reasons. (a) A highly sensitive assay had been developed (17) enabling the pharmacokinetics of CI-941 to be determined in mice at one tenth the LD₁₀ (18). (b) Preclinical pharmacokinetic studies demonstrated that CI-941 pharmacokinetics was linear up to 40 mg/m² (AUC = 110 µM × min), at which dose the AUC was 40% of the AUC at the LD₁₀ (277 µM × min, 52 mg/m²) (18). (c) Plasma protein binding was felt to be sufficiently similar between species to not greatly compromise the interpretation of the pharmacokinetic data (18). In light of these data an attempt was made to apply a PGDE scheme to the Phase I development of CI-941 (19). However, large interpatient variability in CI-941 clearance compromised the application of a PGDE scheme. This paper describes the clinical pharmacokinetics of CI-941 in detail, discusses the problems encountered in adopting a PGDE scheme, and investigates the possible causes for the variability in CI-941 clearance among patients.

MATERIALS AND METHODS

Phase I Evaluation of CI-941. The Phase I evaluation of CI-941 is described in detail elsewhere (19). In brief, patients were selected who had a life expectancy of at least 3 mo and a WHO performance status ≤ 2. Patients with a history of heart disease, hypertension, or a LVEF < 70% were excluded from the trial. Patients received no anticancer therapy 3 wk prior to treatment (and in the case of nitrosoureas and mitomycin C, 6 wk).

Full clinical chemistry and complete blood counts were performed on all patients prior to treatment and then either weekly or twice weekly posttreatment. Liver function was assessed by monitoring rises in the plasma levels of ALT (normal values, < 22 IU/liter) and alkaline phosphatase (normal values, 30 to 133 IU/liter). Renal function (GFR) was assessed by measuring the rate of ⁵¹Cr-EDTA clearance prior to the first course of treatment. The severity of nausea/vomiting and of other toxicities such as myelosuppression, mucositis, and alopecia was scored according to standard WHO protocols (20), and cardiac function was assessed in certain of the patients by monitoring the LVEF (21).

Drug Formulation, Administration, and Sample Collection. CI-941 was obtained from Parke-Davis Pharmaceuticals (Pontypool, Wales) as a lyophilized powder formulated with mannitol (CI-941:mannitol, 1:2). The drug was reconstituted in 0.9% NaCl solution and administered as a single i.v. bolus injection (over approximately 1 to 5 min) via an indwelling cannula. For pharmacokinetic studies, 5- to 10-ml blood samples were collected into heparinized tubes from an indwelling cannula. For pharmacokinetic studies, 5- to 10-ml blood samples were collected into heparinized tubes from an indwelling cannula. For pharmacokinetic studies, 5- to 10-ml blood samples were collected into heparinized tubes from an indwelling cannula.

Plasma Protein Binding. The extent of CI-941 plasma protein binding in individual patients was determined by centrifugal ultrafiltration using ¹⁴C-labeled CI-941. [¹⁴C]CI-941 (specific activity, 220.8 µCi/mg) was a gift from Gödecke Aktiengesellschaft, Freiburg, Germany. The drug was diluted to 25 µg/ml in PBS, and aliquots (22 µl) were added to 550 µl of pretreatment plasma from each patient (final concentration, 2 µM). The supernatant fraction was removed following centrifugation at 1000 × g for 10 min, and 25-µl aliquots were assayed directly for CI-941 by HPLC (17). Recovery of CI-941 was assumed to be complete and, hence, the values may represent an underestimate.

Mauter specimens were obtained from one patient treated at 20 mg/m² of CI-941 who died 4 days posttreatment from a pulmonary embolism. The tissue samples were stored at −20°C until analysis and processed as described previously (18). Tissue homogenates (10%, w/v) were prepared in 0.1 M Tris/HC1 buffer (pH 7.4), and 1-ml aliquots were precipitated with 1 ml of methanol:acetoni trile (1:1, v/v). The supernatant fraction was removed following centrifugation at 1000 × g for 10 min, and 25-µl aliquots were assayed directly for CI-941 by HPLC (17). Recovery of CI-941 was assumed to be complete and, hence, the values may represent an underestimate.

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Binding Studies with α₁-Acid Glycoprotein. In addition to the plasma protein binding studies, the binding of CI-941 to human α₁-AGP was investigated in vitro. [¹⁴C]CI-941 (1 mg/ml in saline) was diluted in triplicate to 2.5, 25, and 250 µM (total volume, 1.25 ml) in PBS and PBS containing human α₁-AGP (25 µM) (Sigma Chemicals, Ltd., Poole, Dorset, England). The samples were incubated for 15 min at 37°C, and 1-ml aliquots were then ultrafiltered as described above. Non-specific binding to the filter was determined by reference to the appropriate filtered and unfiltered standards, i.e., samples not containing α₁-AGP. Aliquots (100 µl) of the ultrafiltrate were then mixed with 10 ml of scintillant and counted for ¹⁴C by LSC.
RESULTS

A total of 37 patients received 74 courses of CI-941, 26 with pharmacokinetic monitoring. Due to the steep dose lethality relationship and nonlinear pharmacokinetics of CI-941 in mice, an AUC of 110 μM × min at 40 mg/m², i.e., 40% of the LD₁₀ AUC of CI-941, was selected as the target AUC (18). It was proposed that doses should be doubled until the target AUC was achieved and then escalated by a modified Fibonacci scheme until dose-limiting toxicity was encountered. The AUC values were derived by the trapezoidal rule and by integration, using the equation AUC = ΣA/C + B/β + Z/ξ. The AUC values given by the two methods were compared by linear regression analysis and found to be in close agreement (r = 0.998, slope = 0.995 ± 0.13, intercept = 4.0 ± 3).

Pharmacokinetic studies were performed on the three patients entered at the Phase I starting dose (5 mg/m²). However there was large interpatient variability in CI-941 clearance at this dose (AUC = 17, 23, and 54 μM × min) (Table 1; Fig. 2), the latter value being approximately 50% of the target AUC. Doubling the dose for the first escalation step would have resulted in the target AUC being reached or possibly exceeded in the case of the latter patient and, hence, this patient received a second dose at 7.5 mg/m², which produced no increase in AUC (54 μM × min) (Table 1).

A total of 26 patients received pharmacokinetic monitoring following CI-941 treatment (Table 1). The plot of AUC versus
dose showed that there was considerable variation in CI-941 clearance at all dose levels ($r = 0.753$) (Table 1; Fig. 3), which was particularly marked at 15, 20, 30, and 40 mg/m² (Table 1; Fig. 3), where the target AUC was exceeded by more than a factor of four (Table 1). Hence, it was not possible to apply a PGDE scheme, and doses were escalated cautiously in 5-mg/m² increments until the MTD at 55 mg/m² was reached (Fig. 3) (19).

The pharmacokinetic values of four patients with exceptionally high AUC values (Patients 8, 11, 17, and 20) were examined in detail (Table 1 and Table 2). As in the total patient population, in these four patients the $\alpha$-phase was the single most important contributor to the AUC (47 to 55%); thus, no single phase was responsible for the abnormally high AUC values (Table 2). Further studies, to identify the cause of the variability in CI-941 clearance, examined differences in plasma protein binding. These binding studies revealed extensive protein binding ($95 \pm 1\%$), with no marked differences between patients (Table 1). Furthermore, although CI-941 did bind to $\alpha_1$-AGP the extent of binding was limited ($67 \pm 6\%$) even in the presence of a 10-fold $\alpha_1$-AGP excess (Table 3), indicating that elevated levels of $\alpha_1$-AGP levels in patients would be unlikely to influence the overall protein binding and, hence, the clearance of CI-941.

CI-941 displayed triphasic plasma pharmacokinetics in patients (Fig. 4), with $t_{\text{m}}$ values of $7.6 \pm 2$ min, $65 \pm 27$ min, and $21 \pm 9$ h for the $\alpha$, $\beta$, and $\gamma$ phases, respectively (Table 1). Tissue distribution studies, performed in one patient who died 4 days posttreatment at 20 mg/m² from a pulmonary embolism, revealed that over 5% of the total dose was present in the liver (Table 4). CI-941 was also detected in the heart, spleen, and pancreas, but was below the limit of detection (<100 ng/g) in the lung, thyroid, kidney, and tumor specimens (Table 4).

DISCUSSION

Pharmacokinetically guided dose escalation strategies have been applied during the Phase I evaluation of several new anticancer drugs including the macrocyclic lactone rhizoxin (26), the anthrapyrazole pirozantrone (27, 28), and the anthra-cycline I-DOX (29). These studies have had varying degrees of success. Comparative pharmacokinetic studies with rhizoxin in mice and patients demonstrated that the plasma AUC values in patients (0.45 to 1 $\mu$M x min) were markedly lower at the MTD than the levels attained at the LD10 in mice (44 $\mu$M x min) (26). The application of a pharmacokinetically guided dose escalation scheme was also not possible due to failure to

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**Table 2** Contribution of the $\alpha$, $\beta$, and $\gamma$ phases of CI-941 clearance to the total CI-941 AUC

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (mg/m²)</th>
<th>TOTAL AUC ($\mu$M x min)</th>
<th>$\alpha$ phase</th>
<th>$\beta$ phase</th>
<th>$\gamma$ phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>26</td>
<td>36</td>
<td>28</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>44</td>
<td>28</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>88</td>
<td>54</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>136</td>
<td>48</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>91</td>
<td>67</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>456</td>
<td>47</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>199</td>
<td>55</td>
<td>23</td>
<td>22</td>
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<td>9</td>
<td>45</td>
<td>469</td>
<td>49</td>
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<td>18</td>
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<td>10</td>
<td>50</td>
<td>288</td>
<td>59</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>11</td>
<td>55</td>
<td>367</td>
<td>51</td>
<td>15</td>
<td>34</td>
</tr>
</tbody>
</table>

Mean ± SD $58 \pm 11$, $18 \pm 6$, $24 \pm 8$.

---

**Table 3** Binding of $[^{14}C]$CI-941 to $\alpha_1$-acidic Glycoprotein (25 $\mu$M)

<table>
<thead>
<tr>
<th>[CI-941 concentration ($\mu$M)</th>
<th>% bound*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>67 ± 6*</td>
</tr>
<tr>
<td>25</td>
<td>27 ± 3</td>
</tr>
<tr>
<td>250</td>
<td>11 ± 3</td>
</tr>
</tbody>
</table>

* Corrected for nonspecific binding to the filter.

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**Fig. 4** Plasma CI-941 levels in a patient treated at 45 mg/m².
detect the drug at the starting dose despite the availability of a highly sensitive assay (26). PGDE schemes have been more successful with the anthrapyrazole pirozantrone (27, 28). In these studies it was demonstrated that the MTD was reached with one less dose escalation than would have been required using conventional dose escalation schemes (27, 28). However, a number of problems were apparent from the studies with pirozantrone. The first problem was that drug levels could not be adequately measured at the starting dose; hence, the initial dose escalation was chosen empirically. The second problem was that there was substantial variability in plasma pirozantrone clearance (25%) among patients (27, 28). Perhaps the most successful application of PGDE to date has been the Phase I study of I-DOX by Gianni et al. (29). Initial studies demonstrated marked interspecies differences in the metabolism of I-DOX to I-DOXOL. I-DOX was rapidly metabolized in patients by an aldo-keto reductase which was absent in mice. Consequently, initial doses were escalated by a modified Fibonacci scheme. Subsequent studies revealed that I-DOX and I-DOXOL were equicytotoxic; hence, the target AUC could then be adjusted to be the sum of I-DOX and I-DOXOL AUCs at the I-DOX LD10 (29). A PGDE scheme was successfully applied to the remainder of the trial, and the AUC at the human MTD was found to be 71% of the AUC at the mouse LD10 (29).

The study reported herein examines the pharmacokinetics of the anthrapyrazole CI-941 in patients and examines why a PGDE scheme could not be applied to the Phase I development of this drug. A starting dose of 5 mg/m2, based on one tenth the LD10 in mice (18), was found to be a safe starting dose (19). Having established the AUC at this dose, the intent was to apply a PGDE scheme based on achieving a target AUC of 110 µM x min (18). However, the large interpatient variability in CI-941 clearance at the starting dose (AUC values, 17, 23, and 54 µM x min, respectively; Table 1) made the application of PGDE strategy impractical (19). Patient 3 (AUC = 54 µM x min) had an AUC value approximately 50% of the target AUC (110 µM x min) (Table 1; Fig. 2). Conversely, Patient 2 (AUC = 17 µM x min) cleared the drug from the plasma so rapidly (clearance = 554 ml/min/m2) that the phase was below the limit of detection of the assay (1 ng/ml) (Table 1; Fig. 2). Hence, extrapolation of the AUC data that accrued at the first dose level indicated that the target AUC could be achieved at any dose between 10 mg/m2 and 25 mg/m2. Pharmacokinetic studies performed at 10 mg/m2 showed that there was still substantial interpatient variability in drug clearance and, hence, it was decided to escalate the dose in 5-mg/m2 dose increments until the MTD was reached.

Pharmacokinetic analysis on a total of 26 patients over the dose range of 5 to 55 mg/m2 showed that there was considerable variability in drug clearance at all dose levels (clearance = 417 ± 194 ml/min/m2) (Table 1). The pharmacokinetic data could best be described by a three-compartment open model as was the case for the pharmacokinetics of CI-941 in mice (18). Analysis of patients with markedly high AUC values, i.e., ≥ mouse LD10 AUC, revealed that no single phase was responsible for this variability (Table 2). For the overall patient population, the phase was the major contributor to the total AUC (58 ± 11%), with the and phases at 18 ± 6% and 24 ± 8% total AUC, respectively (Table 2).

Although there was a good overall agreement between the mouse LD10 (52 mg/m2) and the human MTD (55 mg/m2) (18, 19), there were marked interpatient variability in CI-941 clearance and only a weak correlation between dose and AUC (r = 0.753) (Fig. 3). There was no correlation between pretreatment GFR and CI-941 clearance (r = 0.155; P > 0.05, not significant (Fig. 5A) which is not surprising as urinary excretion accounts for only 5.2 ± 2.8% of the dose 24 h posttreatment. Furthermore, as evidenced by the failure to detect CI-941 plasma metabolites in patients by HPLC, the drug does not appear to be extensively metabolized in vivo. Lack of circulating metabolites in patients is in agreement with [14C]CI-941 metabolism studies performed in mice where no major plasma metabolites were detected (30). Hence, it is unlikely that metabolism signifi-

Table 4  Cl-941 tissue distribution in autopsy specimens in a patient treated at 20 mg/m2 of Cl-941

<table>
<thead>
<tr>
<th>Organ</th>
<th>Cl-941 (ng/g of wet wt)</th>
<th>Dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>950 ± 27*</td>
<td>5.20 ± 0.2</td>
</tr>
<tr>
<td>Heart</td>
<td>250 ± 167</td>
<td>0.24 ± 0.1</td>
</tr>
<tr>
<td>Spleen</td>
<td>421 ± 158</td>
<td>0.24 ± 0.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>367 ± 45</td>
<td>0.06 ± 0.01</td>
</tr>
<tr>
<td>Lung</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Thyroid</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Kidney</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Tumor</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Mean ± SD of three observations.

ND, below the limit of detection (i.e., <100 ng/g).
CLINICAL PHARMACOKINETICS OF THE ANTHrapyrazole CI-941

tially accounts for the interpatient variability in CI-941 clearance.

Although hepatic metabolism may not be important in CI-941 clearance, biliary excretion could play an important role (31). Analysis of hepatic function suggests that there may be an association between elevated pretreatment ALT and alkaline phosphatase levels and low CI-941 clearance (Fig. 5, B and C), although the number of patients in this study was small. In addition, plasma ALT levels are only a crude index of liver function, in particular biliary function, and alkaline phosphatase levels can be elevated in patients with metastatic liver disease or patients with bone metastases. Considering these limitations, no firm conclusions should be drawn with regard to drug clearance and hepatic function, although further studies are warranted.

Plasma protein binding has been identified as an important factor to consider when extrapolating pharmacokinetic data from experimental animals to humans (9). For example, the plasma protein binding of flavone acetic acid in mouse and human plasma has been compared in an attempt to account for the poor antitumor activity of this agent in patients (32). Recently, the binding of drugs to α₁-AGP has attracted considerable attention. α₁-AGP is an acute-phase protein that binds basic drugs which can be elevated in certain cancer patients. Variations in α₁-AGP levels could therefore be a factor which may contribute to interpatient variability in drug clearance for agents which bind to this constituent (33–35).

Studies were undertaken to examine interpatient differences in plasma protein binding and, in particular, whether or not binding to α₁-AGP could modulate the rate of CI-941 clearance from plasma. There was no marked difference in plasma protein binding (95 ± 1%; Table 1) among patients and, although CI-941 did bind to α₁-AGP (Table 3), only 27 ± 3% of the total drug was bound at equimolar concentrations. Even in the presence of a 10-fold excess of α₁-AGP, only 67 ± 6% of the drug was bound. Despite the high degree of protein binding in both mouse (80 to 84%) and patient plasma (95 ± 1%), the tissue distribution studies in mice demonstrated high tissue/plasma concentration ratios (18). Consequently, it can be concluded that plasma protein binding of CI-941 is unlikely to influence the tissue distribution of the drug or the overall pharmacokinetics of CI-941.

This study has shown that, although the mouse LD₅₀ AUC and the human MTD AUC were similar, interpatient variability in drug clearance can compromise the application of a pharmacokinetically guided dose escalation scheme. Detailed pharmacokinetic analyses failed to clearly identify the reason for the variability in CI-941 plasma clearance, although there was a suggestion of impaired clearance in patients with elevated liver function tests. Further prospective studies are warranted to assess the utility of PGDE strategies and to determine whether or not the variability encountered in drug clearance is unique to CI-941. Importantly, preliminary results show promising signs of high-level antitumor activity in breast cancer patients (36), a finding which argues strongly for the further clinical evaluation of CI-941.

REFERENCES


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