Antitumor Efficacy of PD115934 (NSC 366140) against Solid Tumors of Mice

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ABSTRACT

PD115934 (NSC 366140) is a soluble pyrazoloacridine derivative presently undergoing preclinical toxicology evaluation with the anticipation of Phase I human investigation. The agent displayed both human and murine solid tumor selectivity in vitro in a soft agar disk diffusion assay, relative to its activity against murine L1210 leukemia. In vivo it was highly active against solid tumors colon adenocarcinoma 38 and pancreas ductal carcinoma 03, which was consistent with the cellular cytotoxicity seen in the disk diffusion assay. A log cell kill of >4.0 was demonstrated in vivo against both models.

PD115934 was administered by both bolus and infusional therapy. After completion of these trials, it was determined that this compound was a schedule category III agent, i.e., a schedule-independent agent with peak plasma level toxicity. The main toxicity encountered with infusional therapy was myelosuppression. With bolus therapy, central nervous system toxicities were dose limiting. On the basis of our preclinical infusion studies, we recommend a 2-h infusion twice weekly in humans in order to obtain a total dose of 360 mg/m2 over 8 weeks.

INTRODUCTION

The pyrazoloacridine derivative PD115934 [NSC366140; 9-methoxy-N,N-dimethyl-5-nitropyrazolo(3,4,5-k)acridine-2(6H)-propanamine] (Fig. 1) has recently been recommended by the Decision Network Committee of the National Cancer Institute for preclinical toxicology evaluation with the anticipation of Phase I human investigation. Our interest in the agent began in 1985 when Wozniak discovered that the agent was one of three in a series of nitroaridines that had selective solid tumor cytotoxicity (compared to leukemia cells) in a soft agar disk diffusion assay (unpublished results). The solid tumor selectivity was also confirmed by in vivo testing against pancreatic ductal adenocarcinoma 03. These results were readily reproduced and extended to a variety of tumors (1-3).

In vitro, the agent demonstrated favorable activity against hypoxic, noncycling, and Adriamycin-resistant cells with preferential inhibition of RNA synthesis (1-3). In vivo evaluations carried out at the Warner-Lambert company demonstrated significant activity against colon adenocarcinoma 11/A, mammary adenocarcinoma 16/C, FD-1 adrenal osteogenic sarcoma, B16 melanoma/ADR, L1210 leukemia, and P388 leukemia. In vivo, it was inactive against mammary adenocarcinoma 16/C Adriamycin, M5076 sarcoma, P388/Adriamycin, B16 melanoma, MX-1 adenocarcinoma, A549 lung adenocarcinoma, and LOX amelanotic melanoma (1-3).

PD115934 is not without limitations, however. These limitations include CNS3 toxicity with high bolus "rapid-push" dosages of the agent. The work reported herein involves dose/schedule studies designed to circumvent the CNS toxicity problem and suggests a schedule suitable for clinical application.

MATERIALS AND METHODS

Mice

Indbred C57BL/6, C3H/He, BALB/c, and DBA/2 and hybrid C57BL/6 × DBA/2 (heretofore called B6D2F1) and BALB/c × DBA/2 (hereafter called CD2F1) mice were bred in house from strains obtained from the Frederick Cancer Research Facility, Frederick, MD.

Tumors

Murine Tumors. The following transplantable solid tumors of mice were used for in vitro and/or in vivo testing: pancreatic ductal adenocarcinoma 02; pancreatic ductal adenocarcinoma 03; colon adenocarcinomas 38 (5-8) and 51/A (5); and mammary adenocarcinoma 16/C/Adriamycin, M5076 sarcoma, P388/Adriamycin, B16 melanoma, MX-1 adenocarcinoma, A549 lung adenocarcinoma, and LOX amelanotic melanoma (1-3).

Antitumor Agent

PD115934 [NSC366140; 9-methoxy-N,N-dimethyl-5-nitropyrazolo(3,4,5-k)acridine-2(6H)-propanamine] was obtained from Chemotherapy Department, Parke-Davis Pharmaceutical Research Division. The compound easily dissolved in distilled water.

In Vitro Studies

Soft-Agar Colony Formation Disk Diffusion Assay for the Determination of Selective Cytotoxicity for Different Tumor Types

For this assay, L1210 leukemia and solid tumor cells were plated in soft agar. The drug was placed on a filter paper disk, which was then placed on top of the soft agar containing the tumor cells (9-13).

For the L1210/solid tumor differential assay, a hard bottom layer [containing tryptic soy broth (0.8%), Noble agar (0.8%), media (CMRL/Fischer's, 50%/50%), and horse serum (11%) at 48°C] was poured into 60-mm plastic dishes (3 ml in each), allowed to solidify, and stored at 37°C in 5% CO2. Bottom layers were used 4-10 days after preparation. A soft agar top layer, containing Noble agar (0.44%), media (CMRL/Fischer's, 50%/50%), and horse serum (11%), and titered tumor cells was placed on top of the solid tumor cells (9-13).

The abbreviations used include: CNS3, central nervous system; CMRL, Connaught Medical Research Laboratories; pan 03, pancreatic ductal carcinoma 03; T/C, size of treated tumor/size of control tumor; HNTD, highest non-toxic dose.
where \( a \) and \( b \) are the tumor length and width (mm), respectively.

Tumor weights were estimated from two-dimensional measurements:

\[
\text{Tumor weight (mg)} = \frac{a \times b^2}{2}
\]

where \( a \) and \( b \) are the tumor length and width (mm), respectively.

**Cell Preparation**

Both the mouse solid tumors and the leukemia L1210 were passaged s.c. in the appropriate inbred mice. Cells for the in vitro assay were derived directly from these s.c. passage tumors. The tumors (800 to 1500 mg) were cut into 200–300-mg fragments in 10–15 ml of cold Hank’s basal salt solution containing 10% horse serum. The tumor was disrupted using a Stomacher-80 for 15 s. This material was then poured through a 100 mesh sieve. Residual material was forced through (by finger with a sterile glove) and the sieve was rinsed with cold media. The material was then drawn up (rapidly) and pushed down (slowly) in a 5-ml glass syringe (without a needle) and again poured through a sieve without forcing material through (with one rinse). The cell suspension was centrifuged twice at 150 \( \times \) g for 5 min in cold CMRL/Fischer’s media with 11% horse serum. Plating efficiencies varied from one tumor type to another and colonies arose from varying size clumps of cells as well as single cells. Titers were adjusted to produce 300–1000 colonies/60-mm disk.

A volume of 0.05 ml of each drug dilution in ethanol was added to 6.5-mm disks (standard hole punch of Whatman No. 1 filter paper). The disks were allowed to dry and then placed one-third of the distance from the edge of the tumor-containing dish. The plates were incubated for 6–10 days and examined on an inverted microscope (\( \times 40 \)). Depending upon the innate sensitivity of the cells for the drug (and the concentration of the drug) a zone of inhibition of colony formation occurred. The zone of inhibition (measured from the edge of the disk to the first colonies) was determined in units; 200 units = 6.5 mm (the size of the filter paper disk).

**In Vivo Studies**

**Chemotherapy**

The methods of protocol design, tumor transplantation, drug treatment, end point determination, definition of terms, toxicity evaluation, data analysis, quantification of tumor cell kill, and the biological significance of the drug treatment results with transplantable tumors have been presented (6–8, 10, 12, 13). The following is a brief summary of those methods as they apply to the work described.

Because of limited supplies of PD115934 and to help ensure a more uniform tumor burden per mouse (thus reducing the requirement for greater numbers of mice per group), bilateral tumor implants were used. The animals necessary to begin an experiment were pooled, implanted bilaterally s.c. on day 0 with 30–60-mg tumor fragments using a 12-gauge trocar, and again pooled before randomization to the various treatment and control groups. Chemotherapy was either started within 3 days after tumor implantation while the number of cells per mouse was relatively small (\( 1 \times 10^7 \)–1 \( \times 10^8 \) cells), or allowed to grow to palpation (2–4 \( \times 10^8 \) cells) in a more advanced stage trial.

Tumors were measured with a caliper once or twice weekly (as needed) until either tumors exceeded 1600 mg or cure was assured. Tumor weights were estimated from two-dimensional measurements:

\[
\text{Tumor wt (mg)} = \frac{a \times b^2}{2}
\]

**End Points for Assessing Antitumor Activity**

The following quantitative end points were used to assess antitumor activity:

**Tumor Growth Delay.** In \( T - C \), \( T \) is the median time (in days) required for the treatment group tumors to reach a predetermined size, and \( C \) is the median time (in days) for the control group tumors to reach the same size. Tumor-free survivors were excluded from these calculations (cures were tabulated separately).

**Calculation of Tumor Cell Kill.** For s.c. growing tumors, the log\(_10\) cell kill was calculated as:

\[
\log_{10} \text{cell kill (total)} = \frac{T - C}{(3.32)}(T_d)
\]

where \( T - C \) is the tumor growth delay (in days) as described above and \( T_d \) is the tumor volume-doubling time (in days), the latter estimated from the best fit straight line from a log-linear growth plot of the control group tumors in exponential growth (500–1500-mg range). The conversion of the \( T - C \) values to \( \log_{10} \) cell kill is possible because the \( T_d \) for tumors regrowing posttreatment approximated the \( T_d \) values of the tumors in untreated control mice.

**Determination of Activity by Tumor Growth Inhibition (T/C Value).** Measurements were carried out simultaneously in both the treatment and control groups. When the control group tumors reached a weight of approximately 750–1500 mg (median of group), the median tumor weight of each group was determined (including zeros). The T/C value in percentage is an indication of antitumor effectiveness. A T/C equal to or less than 42% is considered significant antitumor activity. A T/C value <10% is indicative of a high degree of antitumor activity and is the level used by the National Cancer Institute to justify further development if other requirements are met (termed DN-2 level activity).

A weight loss nadir of 20%/mouse or greater (mean of group) or 20% or more drug deaths is considered an excessively toxic dosage. Animal body weights included the weights of the tumors.

**Schedule of Administration.** PD115934 was found to be a schedule category 3 agent. In other words, it was schedule independent but had a peak plasma level effect which causes immediate postinjection toxicities (14). With this category of drug, the total dose at the apparent maximum tolerated level appears to increase as the number of injections increase within the 10-day period. This phenomenon is usually caused by an intolerance to a high plasma level of the drug and results in immediate postinjection death. The schedule producing immediate death is not satisfactory for the evaluation of antitumor activity. In this category, efficacy (for a sensitive tumor) correlates with the total dose that can be administered. Dose splitting (or infusion schedules) allows a higher total dose to be tolerated and thus an apparent improvement in efficacy.

**Table 1 experimentally defined PD115934 as a category 3 agent. As can be seen, the maximum tolerated total dose was less than 240 mg/kg. This dose could not be administered as a single bolus but rather as much smaller frequent injections secondary to acute peak plasma level toxicity. Also, an infusional schedule was carried out in that trial. A much higher total dose per injection (21.5 mg/kg/injection versus 100 mg/kg/injection) was administered without the development of acute toxicity.**

**Infusional Technique**

The lateral tail vein was cannulated with a 24-gauge 0.75-inch radiopaque Teflon catheter (Burron Medical, Inc., Bethlehem, PA). Prior to cannulation, the catheter was flushed with a 1% polyoxyethylene sorbitan monopalmitate 40-1% heparin solution. When adequate blood return was noted, the guide was removed and the extension tubing was attached to the catheter. The drug was loaded into a 3-ml syringe (Becton Dickinson, Rutherford, NJ) and the extension tubing (20-inch clear plastic tubing, 0.6-ml volume, Medex, Inc., Hilliard, OH) was loaded with normal saline. The drug was infused via a Harvard pump. This infusional technique is an addition to previous techniques as defined by Paul and Dave (15) as well as Grindecy et al. (16).
Peripheral Smears

Blood cell counts from each of the infusionally treated arms, as well as the control arm, were investigated. Blood smears from three separate mice in each arm were examined every other day after therapy initiation. A mean was obtained from the smears. The nadir of blood counts (day of lowest counts) was identified as day 17 (see Table 2). The blood smears were obtained from mice treated on day 10 and 14 with a 1-degree and 4-degree infusion.

Toxicity Studies

Toxicity was examined in both non-tumor-bearing and tumor-bearing mice. Non-tumor-bearing mice were utilized in trials conducted to identify for delayed toxicity. All non-tumor-bearing mice were B6D2F, females (for both bolus and infusional schedules). They were all maintained through day 180 (of trial onset).

RESULTS

In Vitro Evaluation of PD115934

PD115934 was evaluated in the soft agar disk diffusion assay that is used for drug discovery in our laboratory. In this assay, PD115934 was selectively cytotoxic for solid tumors over leukemia L1210 (Table 3). A zone of inhibition of differential of 725 zone units was seen in Colon 38 and Pan 03 (zone unit = 250 zone units = 6.5 mm). The larger the zone, the greater is the cytotoxicity. Data verified with a repeat trial.

Table 2 Hematological toxicity of PD115934 administered by infusion (at nadir)

<table>
<thead>
<tr>
<th>Concentration (mg/kg)</th>
<th>B.W.T.&lt;10%</th>
<th>B.W.T.&lt;20%</th>
<th>B.W.T.&lt;40%</th>
<th>B.W.T.&lt;60%</th>
<th>B.W.T.&lt;80%</th>
<th>B.W.T.&lt;100%</th>
<th>Control 1</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg/kg</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>1.5 mg/kg</td>
<td>15</td>
<td>25</td>
<td>35</td>
<td>45</td>
<td>55</td>
<td>65</td>
<td>75</td>
<td>85</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td>90</td>
</tr>
</tbody>
</table>

PD115934 was administered to mice with both early staged and upstaged disease. The maximum tolerated dose, regardless of schedule, ranged from 112 to 120 mg/kg total dose.

Mice with early staged disease were treated with a variety of schedules [twice daily days 13–11, every other day for 5 treatments, 6-h infusion every 4 days for 3 treatments (Table 1)]. Regardless of schedule, early-staged colon 38 was extremely responsive to PD115934 demonstrating 60–80% cures at the HNTD with >4.0 log-cell kill with each schedule.

Mice with upstaged disease were treated with a once a day days 7, 9, 11, and 13 schedule (Table 4). Upstaged, this tumor was also very responsive to this compound with 20% cures at 88 days and a >4.0 log cell kill.

Table 3 Cytotoxicity of PD115934 in the disk diffusion colony formation assay

<table>
<thead>
<tr>
<th>Concentration (mg/disk)</th>
<th>Mouse tumors</th>
<th>Human tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>75</td>
<td>800</td>
</tr>
<tr>
<td>10</td>
<td>80–200</td>
<td>N/T</td>
</tr>
<tr>
<td>15</td>
<td>40–170</td>
<td>N/T</td>
</tr>
<tr>
<td>70–150</td>
<td>620</td>
<td>N/T</td>
</tr>
</tbody>
</table>

PD115934 (Warner Lambert); orange pellet-powder: 3% ethanol: 1% polyoxyethylenesorbitan monopalmitate 40; 96% distilled H2O; pH 7.0; stable solution; 0.2 ml/injection.

Mouse tumors

Human tumors

N/T, not tested at these concentrations.

Mouse tumors

Human tumors

Mice with upstaged disease were treated with a once a day days 7, 9, 11, and 13 schedule (Table 4). Upstaged, this tumor was also very responsive to this compound with 20% cures at 88 days and a >4.0 log cell kill.
7). At the HNTD a T/C of 13% was obtained. PD115934 demonstrated activity against this tumor.

Toxicity

PD115934 is a solid tumor-selective category 3 agent. It is schedule independent; however, acute toxicities from i.v. bolus administration of doses >30 mg/kg suggest peak plasma level toxicities.

The dose-limiting toxicity with bolus injection was CNS toxicity. Mice (at bolus dosages >30 mg/kg/injection), within 10–15 s postinjection, would go into frank seizure activity. If they did not die secondary to the injection, nonresponsiveness was evident for approximately 10 min followed by stupor then lethargy for approximately 30 min. Afterwards, the mice normalized without clinical evidence of delayed CNS toxicity. There was no adaptation to this toxicity. The drug had to be administered very slowly i.v. in a minimum of 0.4 ml fluid for tolerance of the 25-30-mg/kg/injection bolus doses.

The dose-limiting toxicity with infusional therapy was myelosuppression. Mice did not have the CNS toxicities as noted with bolus injection. Mice, after 1 h infusion, were quite tremulous but the mice in the 4-h infusion had no CNS toxicity. At the highest nonlethal dose, 84 mg/kg, myelosuppression was

Table 4 Treatment of upstaged colon 38 with i.v. PD115934

<table>
<thead>
<tr>
<th>Dose (mg/kg/injection)</th>
<th>Schedule</th>
<th>Total dose (mg/kg)</th>
<th>Body wt change between days 7 and 14 (g/mouse)</th>
<th>Drug deaths (days)</th>
<th>Median tumor burden (mg/mouse) on day 21 (range)</th>
<th>T/C (%)</th>
<th>Tumor free day 88</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
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<tr>
<td>28.0</td>
<td>Days 7, 9, 11, 13</td>
<td>112.0</td>
<td>+1.4</td>
<td>0/5</td>
<td>2109 (1661–2327)</td>
<td>0</td>
<td>1/5</td>
<td>LD50 toxic</td>
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<tr>
<td>21.4</td>
<td></td>
<td></td>
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<td>14.3</td>
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* Colon adenocarcinoma 38, passage 81; BD2F, males; date of birth, 12/20/88; date of arrival, 1/21/89; date of trocar, 3/3/89. PD115934 orange powder-3% ethanol, 1% polyoxyethylenesorbitan monopalmitate 40, 96% distilled H2O, stable solution.

Table 5 Treatment of upstaged colon 31A with i.v. PD115934

<table>
<thead>
<tr>
<th>Dose (mg/kg/injection)</th>
<th>Schedule</th>
<th>Total dose (mg/kg)</th>
<th>Body wt change between days 5 and 11 (g/mouse)</th>
<th>Drug deaths (days)</th>
<th>Median tumor burden (mg/mouse) on day 17 (range)</th>
<th>T/C (%)</th>
<th>Comments</th>
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</thead>
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<tr>
<td>Control</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>25</td>
<td>Days 5, 7, 9</td>
<td>75</td>
<td>+0.9</td>
<td>1/5</td>
<td>356 (63–587)</td>
<td>19</td>
<td>HTD-active log cell kill 0.5</td>
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<tr>
<td>17</td>
<td></td>
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<td>11</td>
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* This trial was a subset of a combination chemotherapy trial. Hence, the inconsistent total dose compared to other trials. The trial was terminated after day 9, secondary to profound toxicity in the combination arms.

Table 6 Treatment of upstaged pancreatic ductal carcinoma 03 with i.v. administered PD115934

<table>
<thead>
<tr>
<th>Dose (mg/kg/injection)</th>
<th>Schedule</th>
<th>Total dose (mg/kg)</th>
<th>Body wt change between days 10 and 19 (g/mouse)</th>
<th>Drug deaths</th>
<th>Days of death</th>
<th>Median tumor burden (mg/mouse) on day 19 (range)</th>
<th>T/C (%)</th>
<th>Tumor free day 112</th>
<th>Comments</th>
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<td>Control</td>
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<tr>
<td>36</td>
<td>Days 10, 12, 14, 16, 18</td>
<td>180</td>
<td>+1.7</td>
<td></td>
<td>1153 (850–1392)</td>
<td>0/6</td>
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<td>24</td>
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<tr>
<td>125</td>
<td>1-h infusion, days 10, 14</td>
<td>250</td>
<td>−3.7</td>
<td></td>
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<tr>
<td>125</td>
<td>4-h infusion, days 10, 14</td>
<td>250</td>
<td>−5.8</td>
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<td>84</td>
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* Pancreas ductal carcinoma 03; passage 64. BD2F, males; average weight, 22.5 g; date of birth, 3/6/89; date of arrival, 4/17/89; date of trocar, 4/28/89; source, National Cancer Institute. PD115934 (Source, Parke Davis). Diluent-distilled H2O only. Stable solution. pH 7.0. All tumors palpable at the start of therapy (>100 mg tumor size).

Table 7 Treatment of pancreatic ductal carcinoma 02 with i.v. PD115934

<table>
<thead>
<tr>
<th>Dose (mg/kg/injection)</th>
<th>Schedule</th>
<th>Total dose (mg/kg)</th>
<th>Body wt change between days 1 and 15 (g/mouse)</th>
<th>Drug deaths</th>
<th>Days of death</th>
<th>Median tumor burden (mg/mouse) on day 15 (range)</th>
<th>T/C (%)</th>
<th>Comments</th>
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<td>Control</td>
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</tr>
<tr>
<td>27</td>
<td>Days 2, 4, 6, 8, 10, 12</td>
<td>162</td>
<td>−0.3</td>
<td></td>
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<td>18</td>
<td>Days 2, 4, 6, 8, 10, 12</td>
<td>108</td>
<td>−4.2</td>
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* Acute lethality after drug injection.

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noted 3 days after the last infusion. The white count of those infused over 4 h decreased less severely (Table 2). Lymphocytes were predominantly affected with reverse differential compared to the control. Reticulocytes represented less than 0.1% of the RBC. Although the platelet count was less at 4 h than at 1 h (300 versus >500 10⁶ liter), overall it was not significant.

Weight loss was observed primarily in the toxic dosages of these trials. A >10% weight loss was associated with a toxic dose, with the exception of the 6-h infusional trial. In the 70-mg/kg/6 h infusion arm (210 mg/kg total dose), there was an 11% weight loss, but mice recovered without lethality or delayed toxicity. Weight gain was rapid with mice returning to their normal weight within 4-7 days of nadir.

Gastrointestinal toxicity was noted in the toxic dosages only. Mice developed diarrhea. Diarrhea was ominous and within 24 h the mice died. In several of the lethal dosages, primarily the twice a day and the infusional dosages, the stool developed an orange discoloration, similar to the color of the drug.

PD115934 is also a necrotizing agent. In a few of the trials, i.v. bolus injections were changed over to s.c. because of tail vein damage. When this was done the s.c. sites developed local tissue necrosis. In the infusional trial, several mice developed tail necrosis within 5-7 days after the infusion was completed.

At lethal dosages, necropsies differed slightly between bolus and infusional therapy. With bolus injection, mice had small, rounded livers with small spleens. Bladders were empty with clotted ureters. Kidneys grossly appeared normal. Intestines had a dark yellow serous fluid. With infusional therapy, spleens and livers were smaller than the bolus arms. Livers were pale and mottled. Intestines were dilated with fluid similar in color to the drug. The peritoneal lining also was discolored. Kidneys, bladders, and ureters grossly appeared normal. In several of the mice treated with infusional therapy, the submandibular glands became enlarged (3-4 times normal) and the mice, prior to death, had very swollen faces. This facial appearance occurred only at lethal dosages and all animals with this condition died.

DISCUSSION

PD115934 is one of a new class of anticancer agents known as the pyrazoloacridines. The pyrazoloacridines are a class of antitumor acidines which are characterized by the presence of a 5-nitro substituent (Fig. 2). PD115934 is one of the most potent of the pyrazoloacridines. It possesses a methoxy group at position 9 (Fig. 1). The result of this substitution is solid tumor selectivity. Other substituents at this position, i.e., a hydroxy or pivaloyl ester for example, result in compounds with greater leukemic selectivity.

The results of preclinical in vivo schedule-category trials determined PD115934 to be a schedule category 3 agent; i.e., it is schedule independent with peak plasma level toxicities (11, 14). Single bolus dosages >30 mg/kg were immediately lethal (within 24 h of injection). In order to obtain a meaningful and efficacious total dose (e.g., >100 mg/kg), dose splitting was required. The primary toxicity with bolus administration was CNS. This toxicity was altered with short infusions (Table 6). There was modest CNS toxicity with a 1-h infusion and no CNS toxicity with more prolonged 4- or 6-h infusions. The dose-limiting toxicity was significantly altered with the infusional schedule and became hematological. Based on these results, a short term (i.e., 1-4 h) infusion would appear to be reasonable for humans. The fact that peak plasma problems are more pronounced the smaller the animal, a 1-h infusion in humans may even be feasible. Tail vein necrosis was also noted (although the agent is far less necrotizing than Adriamycin). Thus, a central venous access for infusional therapy in humans is suggested.

One of the more favorable characteristics of this compound was its rapid host recovery time. Mice that developed weight loss or appeared scurfy normalized with 4-7 days after discontinuing therapy. Through day 180, there was no delayed toxicity. The rapid host recovery seen here implies that a frequent schedule of administration; i.e., weekly or twice weekly administration, would be appropriate in humans.

PD115934 is an active agent against murine solid tumors. It demonstrated in vitro activity against colon 38, pancreatic ductal carcinoma 03 and HCT-8. In vivo, it had significant activity against both early and “upstaged” colon 38 and pancreatic carcinoma 03 with minimal activity against colon 51/A and pancreatic carcinoma 02. This solid-tumor efficacy profile, compounded with minimal toxicity, hypoxic cell preference, activity against noncycling cells, and preferential inhibition against RNA synthesis are novel and appealing traits (1-3). The maximum tolerated total dose of this compound in mice was approximately 120 mg/kg (360 mg/m²). Efficacy was demonstrated at this dose. Based on the results of our trials, it may be necessary to reach a total dose of approximately 360 mg/m² in humans in order to achieve efficacy. Our recommendations for clinical trial are short infusional schedules (i.e., 1-4 h) two times per week with single dosages cumulative to 360 mg/m² over a 6-week period.

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Antitumor Efficacy of PD115934 (NSC 366140) against Solid Tumors of Mice

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