Oral Efficacy and Bioavailability of a Novel Taxane

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ABSTRACT

A novel taxane (IDN 5109), originally selected for its ability to overcome P-glycoprotein-mediated drug resistance, is characterized by an improved preclinical profile in terms of efficacy and tolerability. Because P-glycoprotein may critically influence intestinal absorption and oral bioavailability of taxanes, the purpose of the study was to evaluate the bioavailability, the pharmacokinetic behavior, and the antitumor activity of the new taxane after oral administration. A comparative study of antitumor activity of Taxol and IDN 5109 given orally was performed in a human breast carcinoma model, MX-1, which is highly responsive to i.v. treatment with both of the taxanes. In contrast to Taxol, which was completely ineffective after administration to MX-1-bearing mice, oral IDN 5109 exhibited an activity comparable with that of i.v. treatment (i.e., 100% cures). Again, the maximal tolerated doses were comparable (90 mg/kg, every 4 days for four doses) after i.v. and oral treatment. Three other tumor models (LoVo, IGROV/DDP, and U87) with a variable sensitivity to the drug were used to compare the antitumor effects of i.v. and oral treatment with IDN 5109. The efficacy after oral administration was only slightly lower than that found after i.v. treatment at equivalent doses; but optimal effects were comparable likely as a consequence of the long (>6 h) terminal half-life of oral IDN 5109. The bioavailability of IDN 5109 assessed by comparing area-under-the-curve values after oral and i.v. administration was approximately 50%. The oral efficacy of the novel taxane, likely related to the inability of the P-glycoprotein to recognize the drug, which allowed an adequate intestinal absorption, is a unique feature among the taxanes and may represent a pharmacological breakthrough in their clinical use.

INTRODUCTION

Taxanes represent a new class of antitumor drugs endowed with a peculiar mechanism of action, i.e., inhibition of microtubule disassembly (1). The current clinical taxanes, Taxol and Taxotere, are effective against a large number of human tumors, in particular, ovarian and breast carcinomas (2). Both of the drugs have been described as substrates for P-glycoprotein, responsible for the MDR phenotype (3, 4). Besides being involved in mechanisms of tumor cell resistance, P-glycoprotein is overexpressed in the intestinal mucosa and may be relevant in the processes of biliary excretion and fecal elimination and strongly limits oral bioavailability of Taxol (5, 6). Cotreatment with P-glycoprotein inhibitors enhances oral absorption of Taxol (7, 8).

Overcoming MDR represents a goal in the development of novel taxanes, and a series of analogs derived from 14β-hydroxy-10-deacetylbaccatin III has been synthesized and investigated with this purpose (9, 10). The analog IDN 5109 was originally selected as the most promising molecule in the series, and additional preclinical investigations have confirmed the therapeutic interest of the molecule. Improved pharmacological properties and an enlarged spectrum of the antitumor activity of IDN 5109 compared with Taxol have been described in a large panel of human tumor xenografts after i.v. drug treatment (11).

The attractive pharmacological profile and the reduced recognition of IDN 5109 by MDR-related transport systems stimulated interest to investigate its bioavailability and antitumor efficacy after oral delivery. In the present study, the effects of IDN 5109 after i.v. or oral treatment were compared in human tumor xenografts characterized by variable responsiveness to the drug (11). The results indicate that, in contrast to oral Taxol (which was completely inactive), IDN 5109 maintained an antitumor activity comparable with that obtained with parenteral administration. The oral efficacy of IDN 5109 was consistent with a good bioavailability (50%) and a long terminal half-life.

MATERIALS AND METHODS

All of the experiments were carried out using 8–10-week-old athymic Swiss nude mice (Charles River, Calco, Italy). Mice were maintained in laminar flow rooms with constant temperature and humidity. Experimental protocols were approved by the Ethics Committee for Animal Experimentation of the Istituto Nazionale per lo Studio e la Cura dei Tumori according to the

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United Kingdom Coordinating Committee on Cancer Research Guidelines (12).

Taxanes were dissolved in absolute ethanol, Cremophor ELP, and cold 0.9% NaCl solution (5, 5, and 90% of the final volume, respectively), or in Tween 80, absolute ethanol, and 0.9% NaCl solution (10, 10, and 80%, respectively), stored, and handled as described previously (11). Only the Tween 80 formulation was used for oral delivery of IDN 5109.

**Antitumor Activity Studies.** The tumor lines MX-1 (a mammary carcinoma), LoVo (a colon carcinoma), IGROV/DDP (an ovarian carcinoma resistant to cisplatin), and U87 (a glioblastoma) were used. They were maintained in vivo by successive transplants of tumor fragments in animal flanks. The tumors examined expressed low levels of P-glycoprotein.

For chemotherapy experiments, tumor fragments (about 2 × 2 × 2 mm) obtained from tumor lines were used. Each control or drug-treated group included 5 or 6 mice bearing bilateral s.c. tumors. Tumors were implanted on day 0, and tumor growth was followed by biweekly measurements of tumor diameters with a Vernier caliper. TW was calculated according to the formula: TW (mg) = Tumor Volume (mm3)2 × D/2 where d and D are the shortest and the longest diameter, respectively. Drug treatment started when mean TW was 80–100 mg. Drug solutions of 6 mg/ml and 3.6 mg/ml were prepared for IDN 5109 and Taxol, respectively, and different drug doses were administered in variable volumes (10, 13, or 15 ml/kg body weight), with a schedule of every 4 days for four doses (q4 d × 4), unless otherwise stated.

The efficacy of the drug was assessed as: (a) TWI% in drug-treated versus control mice expressed as: TWI% = 100 − (mean TW treated/mean TW control × 100), usually evaluated a week after the end of treatment; and (b) Log10 cell kill (LCK) calculated by the formula: LCK = (T − C)/3.32 × DT where T and C are the mean times (days) required for treated (T) and control (C) tumors, respectively, to reach a predetermined weight, and DT is the tumor doubling time. A LCK value greater than 1 is indicative of an active compound.

For statistical comparison, TW of treated versus control mice was compared over the entire period of observation, using an ANOVA followed by the Newman-Keuls test. P ≤ 0.05 was considered significant.

**Toxicity Studies.** Toxicity was determined in tumor-bearing mice as: (a) body weight (BW) loss calculated as: BWL% = 100 − (mean BWdayx-mean BWday1 × 100), where day 1 is the first day of treatment and day x is any day afterwards. Maximal body weight loss values (Max BWL %) are reported in the Tables; and (b) lethal toxicity, i.e., any death in treated groups occurring before any control death.

**Pharmacokinetic Studies.** Plasma pharmacokinetic studies were carried out in female CDF1 mice (Charles River, Calco, Italy). The drug was formulated in Tween 80 and absolute ethanol as described above. After single i.v. or oral administration, blood samples were taken from four animals per time point at 5, 15, 30, and 45 min and 1, 2, 4, 8, 16, and 24 h. Blood was obtained from retro-orbital plexus under ether anesthesia and collected in heparinated tubes. The plasma fraction was immediately separated by centrifugation at 2000 × g for 10 min at 4°C and stored at −20°C until analysis of IDN 5109 and its 7-epi-form. IDN 5109 was measured by employing a recently developed HPLC assay that is able to determine IDN 5109 and its epi-form, with good degree of sensitivity, precision and accuracy (13). The method involved the addition of a thioderivative of IDN 5109 as internal standard, a totally automated solid-phase extraction on CN cartridges (Waters, Milford, MA), and HPLC separation on a symmetry shield column (Waters, Milford, MA) with a mobile phase of 10 mM NaH2PO4 (pH 5.2)/acetonitrile (47/53). The analytes were detected at 227 nm. The recovery of IDN 5109 and its epi-form from plasma was more than 80 and 75%, respectively. The assay was linear over a concentration range of 0.05–10 μg/ml, and all of the analytical runs performed in 3 days of the validation study had a standard correlation coefficient >0.995. The limit of quantitation for both the analytes is 0.050 μg/ml, with an intra- and interday precision within 5% and an accuracy comprised in the range of 95−107%. Pharmacokinetic parameters were calculated by using a nonlinear fitting program (14). The experimental 24 h AUC i.v. and 24 h AUC oral of IDN 5109 were calculated by the trapezoidal rule, and the deviation was calculated according to the method described by van Asperen et al. (15).

**RESULTS**

**Comparison between Oral Efficacy of IDN 5109 and Taxol.** The MX-1 tumor was chosen for being highly responsive (100% cures) to both of the taxanes when given by i.v. route (11). When the drugs were administered orally, IDN 5109 (90 mg/kg) was still able to cure 100% of mice, whereas Taxol (90 mg/kg) did not show any activity, although delivered at a dose higher than that given by i.v. route (54 mg/kg; Fig. 1).

**Comparison between i.v. and Oral Efficacy of IDN 5109.** As in the previous study, for i.v. delivery, the drug was dissolved in Cremophor (as in standard formulation for clinical use; Ref. 11). However, because Tween 80 is a more standardized vehicle than Cremophor and allows a more linear pharmacokinetics (16), it may be more suitable for clinical development. The investigation on the oral efficacy of IDN 5109 was,
LoVo colon carcinoma was investigated is also reported in Table 1. In no case was its maximal tolerated dose (54 mg/kg) against the tumor achieved by i.v. administration of Taxol at (TWI, between 50 and 60%). For purpose of comparison, the dose (90 mg/kg) of IDN 5109 with both administration routes against the IGROV/DDP tumor, two dose levels were investigated by both routes. A good dose-response relationship was found with particular reference to LCK values. Again, the efficacy achieved by oral 90 mg/kg was closer to that achieved by 60 mg/kg than by 90 mg/kg given i.v. The glioblastoma U87 showed a low responsiveness to the same drug given orally (90 mg/kg) showed a high level of efficacy, toxicity (toxic death and BWL) was comparable. Against the IGROV/DDP tumor, two dose levels were investigated by both routes. A good dose-response relationship was found with particular reference to LCK values. Again, the efficacy achieved by oral 90 mg/kg was closer to that achieved by 60 mg/kg than by 90 mg/kg given i.v. The glioblastoma U87 showed a low responsiveness to the same dose (90 mg/kg) of IDN 5109 with both administration routes (TWI, between 50 and 60%). For purpose of comparison, the antitumor efficacy achieved by i.v. administration of Taxol at its maximal tolerated dose (54 mg/kg) against the tumor models investigated is also reported in Table 1. In no case was the efficacy of oral IDN 5109 lower than that of Taxol.

**Comparison of Drug Efficacy Using Different Schedules of Oral Administration.** LoVo colon carcinoma was chosen to study the effect of administration schedule on drug efficacy (Table 2). A total dose of 360 mg/kg was given to mice by delivering the drug at various doses and intervals. Although all of the regimens were effective, the best activity was obtained with 90 mg/kg given every 4 days for 4 doses, which markedly inhibited tumor growth without toxic deaths. A higher dose, 120 mg/kg delivered every 7 days for 3 doses, was somewhat less active and well tolerated. Using a lower dose level (60 mg/kg), the efficacy was reduced (TWI <80%), but the tolerability was dependent on the treatment intensity (i.e., every 2 days for 6 doses was more toxic than every 4 days for six doses). A low dose, 20 mg/kg, administered daily for 18 days was even less effective.

**Bioavailability and Pharmacokinetics.** Fig. 2 shows the plasma levels of IDN 5109 in CDF-1 mice. After i.v. treatment with 60 mg/kg (Fig. 2A), the drug disappeared in a biphasic fashion with a terminal half-life of 3.5 h. After oral doses, from 30 to 120 mg/kg (Figs. 2, A and B), the peak plasma levels of

<table>
<thead>
<tr>
<th>Tumor (days ± SD)</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>TWI%</th>
<th>LCK</th>
<th>Max BWL%</th>
<th>Tox/tot</th>
</tr>
</thead>
<tbody>
<tr>
<td>LoVo (5 ± 0.2)</td>
<td>60</td>
<td>i.v.</td>
<td>93</td>
<td>3.0</td>
<td>14 (24)</td>
<td>0/5</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>i.v.</td>
<td>97</td>
<td>2.9</td>
<td>10 (17)</td>
<td>0/5</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>p.o.</td>
<td>94</td>
<td>1.8</td>
<td>12 (22)</td>
<td>0/5</td>
</tr>
<tr>
<td></td>
<td>Taxol</td>
<td>i.v.</td>
<td>88</td>
<td>1.5</td>
<td>7 (15)</td>
<td>0/5</td>
</tr>
<tr>
<td>IGROV/DDP (4.7 ± 0.8)</td>
<td>54</td>
<td>i.v.</td>
<td>82</td>
<td>1.2</td>
<td>5 (19)</td>
<td>0/4</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>i.v.</td>
<td>94</td>
<td>1.7</td>
<td>11 (23)</td>
<td>0/4</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>p.o.</td>
<td>76</td>
<td>0.9</td>
<td>2 (17)</td>
<td>0/5</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>p.o.</td>
<td>82</td>
<td>1.1</td>
<td>5 (13)</td>
<td>0/5</td>
</tr>
<tr>
<td></td>
<td>Taxol</td>
<td>i.v.</td>
<td>45</td>
<td>0.4</td>
<td>9 (15)</td>
<td>0/5</td>
</tr>
<tr>
<td>U87 (5.2 ± 2.2)</td>
<td>60</td>
<td>i.v.</td>
<td>47</td>
<td>0.2</td>
<td>11 (19)</td>
<td>0/5</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>i.v.</td>
<td>64</td>
<td>0.5</td>
<td>13 (19)</td>
<td>0/5</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>p.o.</td>
<td>52</td>
<td>0.3</td>
<td>7 (19)</td>
<td>0/5</td>
</tr>
<tr>
<td></td>
<td>Taxol</td>
<td>i.v.</td>
<td>47</td>
<td>0.2</td>
<td>6 (19)</td>
<td>0/5</td>
</tr>
</tbody>
</table>

**Table 1** Comparison of i.v. and oral (p.o.) efficacy of IDN 5109

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Schedule</th>
<th>TWI%</th>
<th>LCK</th>
<th>Max BWL%</th>
<th>Tox/tot</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>qdx18</td>
<td>56</td>
<td>0.5</td>
<td>6 (29)</td>
<td>0/5</td>
</tr>
<tr>
<td>60</td>
<td>q2dx6</td>
<td>71</td>
<td>1.9</td>
<td>20 (24)</td>
<td>1/5</td>
</tr>
<tr>
<td>60</td>
<td>q4dx6</td>
<td>75</td>
<td>0.8</td>
<td>6 (26)</td>
<td>0/5</td>
</tr>
<tr>
<td>90</td>
<td>q4dx4</td>
<td>94</td>
<td>1.8</td>
<td>12 (22)</td>
<td>0/5</td>
</tr>
<tr>
<td>120</td>
<td>q7dx3</td>
<td>89</td>
<td>1.4</td>
<td>4 (22)</td>
<td>0/5</td>
</tr>
</tbody>
</table>

**Table 2** Comparison of different schedules of oral administration of IDN 5109 on LoVo carcinoma.

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Therefore, performed formulating the compound in Tween 80, absolute ethanol, and 0.9% NaCl solution (10, 10, and 80%, respectively). A comparison of antitumor efficacy of i.v. IDN 5109 in the two formulations showed no differences against the LoVo carcinoma. Thus, all of the studies were carried out using the Tween 80 formulation for oral administration and the cremophor formulation for i.v. administration of IDN 5109.

The comparison between i.v. and oral efficacy of IDN 5109 was assessed on three human tumor xenografts, including sensitive (LoVo colon carcinoma and IGROV/DDP ovarian carcinoma) and only moderately responsive (U87 glioblastoma) tumors (Table 1). Against the LoVo tumor, the drug given orally (90 mg/kg) showed a high level of efficacy, only slightly inferior to that achieved by the same i.v. dose and comparable with that achieved by the lower (60 mg/kg) i.v. dose. Toxicity (toxic death and BWL) was comparable. Against the IGROV/DDP tumor, two dose levels were investigated by both routes. A good dose-response relationship was found with particular reference to LCK values. Again, the efficacy achieved by oral 90 mg/kg was closer to that achieved by 60 mg/kg than by 90 mg/kg given i.v. The glioblastoma U87 showed a low responsiveness to the same dose (90 mg/kg) of IDN 5109 with both administration routes (TWI, between 50 and 60%). For purpose of comparison, the antitumor efficacy achieved by i.v. administration of Taxol at its maximal tolerated dose (54 mg/kg) against the tumor models investigated is also reported in Table 1. In no case was the efficacy of oral IDN 5109 lower than that of Taxol.

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**Bioavailability and Pharmacokinetics.** Fig. 2 shows the plasma levels of IDN 5109 in CDF-1 mice. After i.v. treatment with 60 mg/kg (Fig. 2A), the drug disappeared in a biphasic fashion with a terminal half-life of 3.5 h. After oral doses, from 30 to 120 mg/kg (Figs. 2, A and B), the peak plasma levels of...
IDN 5109 were achieved in 15 min, and drug disappearance was slower than after the i.v. route, with elimination half-lives ranging between 6.2 and 8.8 h. The relatively long half-life of IDN 5109 given orally is attributable to the high plasma concentrations of the drug at the late time points.

As shown in Table 3, the bioavailability after oral administration of IDN 5109 ranged between 47 and 62%. Both C_{max} and AUC values seemed to increase proportionally to the dose administered.

**DISCUSSION**

Taxol is a substrate of P-glycoprotein (3), which is known to contribute to drug elimination by mediating biliary excretion and/or limiting reuptake from the intestinal lumen after hepatobiliary excretion (5, 16). Thus, P-glycoprotein plays a role in drug excretion from the circulation into intestinal lumen after i.v. treatment and limits oral absorption of the drug (5, 6). Coadministration of P-glycoprotein inhibitors is required for therapeutic effects of Taxol (7, 8, 17). In agreement with the very low bioavailability of oral Taxol (less than 10%), our study showed a complete lack of antitumor activity of this taxane when given by oral route. In fact, when the oral and i.v. administrations were compared, the optimal antitumor efficacy of IDN 5109 was comparable at the same dose against the MX-1 breast tumor (100% cures by both routes) and the U87 glioblastoma (poorly sensitive; 50/60 TWI%). In the other tumor models investigated, the effects achieved by oral delivery were slightly lower than those achieved by i.v. treatment with the same dose level (90 mg/kg).

After i.v. administration in mice, Taxol has a short plasma terminal half-life of approximately 1 h (18), and this behaviour accounts for a marked increase in activity after intensification of treatment (19, 20). In contrast, the pharmacokinetic studies in mice showed a very long terminal half-life of IDN 5109 in plasma after either oral (more than 6 h) or i.v. (3.5 h) administration. Since the critical factor for tumor response to taxanes seems to be the time-persistence over a critical plasma concentration rather than the AUC values themselves (16, 21), it is likely that, after oral treatment, a critical plasma concentration of IDN 5109 can be reached, and its persistence is sufficient to inhibit tumor growth. This interpretation is consistent with the observation that oral doses of IDN 5109 that are 1.5-fold higher than those used i.v. were sufficient to achieve comparable antitumor efficacy, in spite of a 50% lower AUC after oral compared with i.v. administration. This peculiar behavior may explain the appreciable reduction of drug activity with low daily doses because they do not ensure threshold concentrations required for optimal activity.

The peculiar pharmacokinetic behavior of oral IDN 5109 also accounts for its tolerability at therapeutic dose levels. The

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**Table 3** Main pharmacokinetic parameters of IDN 5109 in CDF1 female mice

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>C_{max} (μg/ml ± SD)</th>
<th>Terminal half-life (h)</th>
<th>F (%)</th>
<th>AUC (0 → ∞) (μg-h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>p.o.</td>
<td>8.5 ± 0.5</td>
<td>7.9</td>
<td>64</td>
<td>33.5</td>
</tr>
<tr>
<td>60</td>
<td>p.o.</td>
<td>12.0 ± 0.3</td>
<td>8.8</td>
<td>49</td>
<td>50.9</td>
</tr>
<tr>
<td>120</td>
<td>p.o.</td>
<td>15.6 ± 3</td>
<td>6.2</td>
<td>37</td>
<td>76.1</td>
</tr>
<tr>
<td>60</td>
<td>i.v.</td>
<td>112.0 ± 17</td>
<td>3.5</td>
<td>3.5</td>
<td>103.9</td>
</tr>
</tbody>
</table>

\[ F = \frac{AUC_{i.v.}}{AUC_{p.o.}} \times \frac{dose \text{ i.v.}}{dose \text{ p.o.}} \]

IDN 5109 were achieved in 15 min, and drug disappearance was slower than after the i.v. route, with elimination half-lives ranging between 6.2 and 8.8 h. The relatively long half-life of IDN 5109 given orally is attributable to the high plasma concentrations of the drug at the late time points.

As shown in Table 3, the bioavailability after oral administration of IDN 5109 ranged between 47 and 62%. Both C_{max} and AUC values seemed to increase proportionally to the dose administered.
maximal tolerated dose orally, according to a every-4-days-for-four doses schedule, was 90 mg/kg, as for the i.v. delivery of the drug (11). Indeed, the observation is consistent with a preliminary myelotoxicity evaluation performed with such a therapeutic dose of IDN 5109. A comparable myelotoxic effect was observed with the i.v. or the oral route (data not shown). An increased incidence of mice presenting a swollen belly after oral as compared with i.v. treatment was observed. In contrast, the reversible neurotoxicity symptoms (i.e., tremor, ataxia) observed with i.v. administration were absent after oral administration, which suggests a somewhat different toxicity profile of IDN 5109 according to whether the route is oral or i.v. A detailed study of preclinical toxicology of oral IDN 5109 is in progress in view of clinical development.

In addition to an improvement in the therapeutic index and antitumor efficacy of IDN 5109 as compared with Taxol after parenteral (i.v.) administration (11), the present results provide evidence of additional pharmacological advantages of the novel taxane analog. Indeed, considering the water insolubility of taxanes, their parenteral use requires formulations with solvents associated with clinical drawbacks. Thus, oral administration would offer obvious advantages for clinical development in terms of reduction of side effects and patient compliance (22).

In conclusion, the study showed that, in contrast to Taxol, the novel taxane IDN 5109 fully maintained its antitumor activity when administered by the oral route, possibly as a consequence of the inability of P-glycoprotein, which is expressed in the gastrointestinal tract, to use the taxane analog as substrate. The oral efficacy of the novel analog is supported by a good bioavailability and by a distinctive pharmacokinetic behavior.

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