First-in-Human Phase 0 Trial of Oral 5-iodo-2-pyrimidinone-2′-deoxyribose (IPdR) in Patients with Advanced Malignancies

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Abstract

Purpose—Iododeoxyuridine (IdUrd), a halogenated nucleoside analog, produced clinical responses when administered as a radiosensitizer via continuous intravenous (c.i.v.) infusion over the course of radiation therapy. We conducted a Phase 0 trial of 5-iodo-2-pyrimidinone-2′-deoxyribose (IPdR), an oral prodrug of IdUrd, in patients with advanced malignances to assess whether the oral route was a feasible alternative to c.i.v. infusion prior to embarking on large-scale clinical trials. Plasma concentrations of IPdR, IdUrd, and other metabolites were measured after a single oral dose of IPdR.

Patients and Methods—Eligible patients had advanced refractory malignancies. A single oral dose of IPdR was administered per patient and patients were followed for 14 days for safety assessments; dose escalations were planned (150, 300, 600, 1200, and 2400 mg) with one patient per dose level (DL) and 6 patients at the highest DL. Blood sampling was performed over a 24-hour period for pharmacokinetic analysis.

Results—There were no drug-related adverse events. Plasma concentrations of IdUrd generally increased as the dose of IPdR escalated from 150 to 2400 mg. All patients at the 2400 mg dose achieved peak IdUrd levels of (mean ± SD) 4.0 µM ± 1.02 µM (25% CV) at 1.67 ± 1.21 hours after IPdR administration.

Conclusions—Adequate plasma levels of IdUrd were obtained to justify proceeding with a Phase I trial of IPdR in combination with radiation. This trial demonstrates the ability of a small, Phase 0 study to provide critical information for decision-making regarding future development of a drug.

Keywords

IPdR; IdUrd; phase 0; clinical trial; pharmacokinetics

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INTRODUCTION

Development of radiosensitizing agents to improve the therapeutic outcome for cancer patients receiving definitive radiation therapy has been a longstanding area of research. Halogenated thymidine (TdR) analogs such as 5-iododeoxyuridine (IdUrd; NSC 39661) and 5-bromodeoxyuridine (BUdR) have been recognized as potential radiosensitizers since the early 1960s (1–3). Cellular uptake and metabolism of these analogs are dependent on the TdR salvage pathway (4). IdUrd produced responses in combination with radiation in Phase I/II clinical trials when given with radiation therapy to patients with high-grade anaplastic astrocytomas and sarcomas (5–7). However, due to the short half-life of IdUrd (in the order of minutes), continuous intravenous (c.i.v.) infusion over the course of radiation therapy was required to maintain adequate exposure (5).

5-iodo-2-pyrimidinone-2′-deoxyribose (IPdR; NSC 726188), an oral prodrug of IdUrd, has many advantages as compared to IdUrd, including ease of administration, a more favorable toxicity profile and a better therapeutic index in animals (8). Oral IPdR would present an attractive alternative to c.i.v. of IdUrd if adequate systemic exposures to IdUrd and its metabolites could be obtained. Here, we conducted a first in human, Phase 0, feasibility trial of IPdR in patients with advanced malignances prior to embarking on large-scale clinical trials of IPdR in combination with radiation therapy. Plasma concentrations of IPdR, IdUrd, and other metabolites were measured after a single oral dose of IPdR. Unlike micro-dosing studies and other variations of the Phase 0 concept, this study was designed to produce concentrations of IdUrd that are expected to be in the therapeutic range, based upon prior clinical studies with c.i.v. IdUrd. Since only a single dose of IPdR was administered, the exposure time to IdUrd is expected to be short, the probability of toxicity is minimized. Establishment of the toxicity profile and the maximum tolerated dose are in the realm of phase 1 studies.

MATERIALS AND METHODS

Eligibility Criteria

Adult patients with advanced malignancies refractory to at least one line of standard treatment were eligible. Patients were 18 years of age or older, had an Eastern Cooperative Oncology Group performance status of 2; and adequate liver, kidney, and marrow function defined as absolute neutrophil count 1,500/μL, platelets 100,000/μL, total bilirubin 1.5 X the upper limit of normal (ULN), aspartate aminotransferase and/or alanine aminotransferase < 3 X ULN, creatinine < 1.5 X ULN. Prior anti-neoplastic therapy must have been completed at least 2 weeks prior to enrollment. Patients unable to swallow pills or those with uncontrolled intercurrent illness or pregnant or lactating were not eligible.

Consent Process

Due to the non-therapeutic nature of the trial, the objectives and the consent form were discussed in detail with potential patients in advance. Patients were asked to verbalize their understanding of the nature of the trial prior to signing the consent form. This trial was conducted under an NCI-sponsored IND with approval from the NCI Institutional Review Board. Protocol design and conduct followed all applicable regulations, guidances, and local policies. ClinicalTrials.gov identifier: NCT01240577.

Study Design

IPdR was supplied by the Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA. A single oral dose of IPdR was administered on day 1, with serial blood and urine sampling performed before and during a 24-hour period after drug

administration for pharmacokinetic (PK) analysis. Patients were followed for 14 days for safety assessments. Oral doses of 150, 300, 600, 1200, and 2400 mg, were explored with one patient enrolled successively to each dose level. At the highest dose (2400 mg), a total of 6 patients were enrolled. A new patient could only be enrolled once the prior patient had completed 2 weeks of participation with no drug related adverse events.

The starting dose of 150 mg was based on 10% of the tolerable dose from a repeat-dose study in the most sensitive animal species, the ferret. There was significant weight loss of 10 to 20% and gastrointestinal side effects in ferrets receiving 1500 mg/kg/day for 14 days.[9] The tolerable dose for repeat dose studies in rats was higher, 2000 mg/kg/day for 28 days.[8] In studies in athymic mice, no significant toxicities were reported after daily oral IPdR doses of   1500 mg/kg/day for 6 to 14 days.

Clinical toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Significant toxicities were defined as toxicities considered to be related to study medication occurring within 14 days of administering IPdR and met the following criteria: a) grade   2 non-hematologic toxicities other than easily correctable electrolyte abnormalities, b) grade   2 thrombocytopenia, c) grade   3 anemia, leucopenia, or neutropenia. If one patient developed significant toxicity, then no additional patients were to be enrolled, the study was to be put on hold, and all the safety and PK data analyzed.

History and physical examination, including performance status and vital signs, were performed at baseline and repeated at the end of 2 weeks. Complete blood counts with differential and serum chemistries were performed at baseline, on day 2, and on day 14 (at off-study).

Pharmacokinetic Evaluations—Peripheral blood samples (7 mL) were collected before and at multiple time points (5, 15, and 30 minutes, 1, 2, 4, 10, and 24 hours) post–IPdR administration. All samples were centrifuged and plasma was stored at −80°C for analysis. Urine (10 mL) was also collected just before drug administration, and then separately at each void; volume measured and recorded, and a sample (10–12 mL) was retained for analysis and stored at −80°C. A sensitive liquid chromatography coupled with tandem mass spectrometry detection (LC–MS/MS) method was developed to measure plasma and urinary concentrations of IPdR, IdUrd, and other metabolites.

Plasma samples were processed by solvent deproteinization, while the urine samples were processed by liquid-liquid extraction. Separation of IPdR and its metabolites was performed on an Agilent 1200LC system (Agilent Technologies, Palo Alto, CA) using a 4.6 x 250 mm Synergi Hydro-RP C18 column. The reference compounds 5-iodo-2-pyrimidinone-2′-deoxyribose (IPdR, NSC726188), 5-iodo-2′-deoxyuridine (IdUrd, NSC39661), 5-iodo-2-pyrimidinone (IP, NSC754229), and 5-iodouracil (IUra, NSC57848) were supplied by the NCI Developmental Therapeutics Program (Bethesda, MD). 5-Bromo-2′-deoxyuridine (BrdUrd) and 5-bromouracil (BrUra) used as internal standards for quantitations were obtained from the Sigma-Aldrich Company (St. Louis, MO). All solvents were HPLC grade. All other reagents were also obtained from the Sigma-Aldrich Company (St. Louis, MO). Calibration curves were constructed by adding known amounts of IPdR, IP, IdUrd, and IUra to control human plasma or to patient pre-dose urine in order to give samples containing concentrations ranging 0.1 to 50 μM of each compound. The response factor was linear over the range of 0.1 to 50 μM. Samples were diluted 1:10 in control matrix and reanalyzed when calculated concentrations exceeded 50 μM. Absolute recoveries of analytes from plasma were 76% for IPdR, 75% for IdUrd, 92% for IUra and 87% for IP. For urine, absolute recoveries of analytes were 92% for IPdR, 93% for IdUrd, and 89% for IUra. The lower

limit of quantitation was 0.1uM for IdUrd and IPdR, and 0.25uM for IP and IUra. Accuracy was found to be greater than 98% for these compounds, with precision of 95%.

RESULTS

A total of 10 patients participated in the study and all patients tolerated study drug well with no drug related adverse events. Patient demographics are presented in Table 1.

Pharmacokinetics

Plasma concentrations of IdUrd, the active metabolite, generally increased as oral doses of IPdR escalated from 150 to 2400 mg (Table 2 and Figure 1). At the highest IPdR dose of 2400 mg, the 6 patients achieved peak IdUrd plasma levels of $4.0 \pm 1.02 \, \mu M$ (25% CV) after 1.67 ± 1.21 hours. Plasma concentrations remained above $1 \, \mu M$ for 3–4 hours, and declined with a half-life of 1.5 hours. For plasma AUC of IdUrd, the CV was 32%.

For the prodrug, IPdR, both Cmax and AUC for plasma were variable at the lower doses that enrolled single patient cohorts (Table 2), including one patient with undetectable levels. At the highest dose, the coefficients of variation for IPdR were 100% for both Cmax and AUC. Both Cmax and AUC for plasma of IUra, the major metabolite, increased more than proportionally as doses were doubled (Table 2 and Figure 2). At the 2400mg dose of IPdR, Cmax values for IUra were $133 \pm 42 \, \mu M$ after 3.3 ± 1.0 hours post IPdR administration (Table 2 and Figure 2). IUra concentrations remained near $100 \, \mu M$ for 10 hours in 4 of 6 patients receiving the 2400 mg dose. The pathways of formation for metabolites of IPdR are presented in Figure 3.

Patient 10 had a history of gastric bypass surgery as part of a bariatric surgery procedure 20 years prior to enrollment on study. Plasma levels of IPdR and its metabolites in this patient were comparable to other patients on the 2400 mg dose.

IPdR and its metabolites, IdUrd, IP, and IUra, were detectable in urine samples from patients receiving 2400 mg of IPdR. Twelve percent ($\pm 8\%$) of the dose was recovered over 24 hours; of the metabolites measured in urine, $90 \pm 13\%$, was IUra.

DISCUSSION

Radiosensitization to improve curative rates in cancer has been an area of ongoing research. Chemotherapies such as fluorouracil (5FU) and gemcitabine have been co-administered to increase the effectiveness of radiation therapy; however, this comes at the cost of increasing toxicities, both systemic and local. Halogenated thymidine analogs have been studied as radiosensitizers and incorporation of their phosphorylated forms into DNA, by DNA polymerase during the process of replication, is necessary for radiosensitization (4, 10). When halogenated thymidine analogs are incorporated into DNA, there is increased sensitivity to damage by the highly reactive uracil free radicals generated by radiation (11). However, due to the short half-life of halogenated analogs, and the need for a high labeling index to derive clinical benefit, c.i.v. administration of such analogs throughout the course of radiation has been evaluated (2, 12–14). IdUrd has shown radiopotentiation in sarcomas and brain tumors with clinical benefit (5, 15–17). A long term study of patients with anaplastic astrocytoma treated with a combination of radiation and IdUrd reported a median survival of 3.2 years, with 33% of patients surviving at 5 years (5). Even though clinical benefit was observed in these trials, the need to administer an agent by c.i.v. infusion over weeks presents practical challenges.

The ability to administer IdUrd orally would circumvent the practical limitations of c.i.v. administration and allow development of this class of agents as potential radiosensitizers. IPdR was formulated as an oral prodrug of IdUrd and, in preclinical models; adequate exposures to IdUrd were obtained following oral administration of IPdR (7, 18). The initial goal of early clinical development of IPdR is to determine safe and effective doses capable of being administered along with radiation. However, prior to proceeding with the definitive dose finding safety study of IPdR with radiation, we conducted a small phase 0 trial of IPdR in patients with advanced malignancies to determine the pharmacokinetics of IPdR and its metabolites in humans.

The data in Table 2, as well as Figures 1 and 2, exhibit substantial differences for IPdR and its metabolites in the patterns for their changes in systemic exposure with dose. Due to the nature of this study design, which intended to minimize the number of patients, it must be recognized that definitive conclusions are not possible. Nonetheless, sufficient information was generated to guide further efforts. In particular, the disproportional increases for IUra exposure in this study are very consistent with prior work that demonstrated disproportional accumulation due to saturation of its metabolic elimination (11). The lack of a consistent pattern for exposure to IPdR is a signal that absorption and/or first-pass metabolism should continue to be monitored in future studies. For the most important compound, IdUrd, the modest variation in both AUC and Cmax among the 6 patients at the highest dose are positive findings for further pursuit of this oral approach. The apparent absence major trends toward disproportional changes in exposure for IdUrd are tempered by the small numbers of patients, but are consistent with larger studies for direct administration of IdUrd (11).

First-in-human 'Phase 0' clinical trials offer an opportunity to evaluate the pharmacology of novel agents in humans well in advance of dose-finding Phase 1 trials. Such trials present a platform for clinical testing of novel compounds with less pharmacology and toxicology data than traditionally required, as drug exposure is limited in Phase 0 trials providing the safety margin (19). Depending on the circumstances, Phase 0 trials can be conducted either under a standard IND or the FDA's exploratory IND guidance (20). Subsequent clinical development decisions can be based on data generated from patient samples rather than solely from preclinical models. Such data can inform drug development decisions including systematic deprioritization of compounds that do not satisfy pre-specified PK or pharmacodynamic criteria.

Previous clinical studies (11,16) have defined a minimum target concentration of 1 μM for IdUrd in plasma. If this phase zero study had found that oral dosing with IPdR could not reach this target concentration of IdUrd, then it would be futile to continue further trials. Because the mean Cmax of IdUrd in plasma was 4.0 μM for the 6 patients at the 2400 mg dose, we can move ahead to consideration of the second drug delivery question: What is the optimal pattern for exposure to IdUrd? Prior work showed that prolonged exposure to IdUrd is essential to derive therapeutic benefit, and continuous infusions have been for 2–4 weeks have been utilized in most clinical studies of IdUrd. However, the length of exposure or time sequence with once-a-day radiation treatment remains largely unexplored. Given the ease of administration of oral IPdR, clinical trials of IPdR in combination with radiation could easily evaluate various sequences and durations of exposure to optimize the therapeutic index of this radiosensitizer. Initiating the clinical evaluation of IPdR with dosing once per day would be a reasonable strategy to generate initial safety data in combination with prolonged periods of radiation. This approach could be followed with dosing twice per day, which would reduce the length of time below the nominal target concentration. Pharmacodynamic studies or diagnostic approaches, as described below, could be combined with clinical assessments to determine the preferred schedule.

When IdUrd was first assessed as a chemotherapeutic, Calabresi et al reported tumor shrinkage in 6 out of 11 patients treated with c.i.v. (2). In 4 of 9 patients treated with intrahepatic arterial infusions of IdUrd, Cheng et al reported tumor shrinkage to be between 40 to 65% (13). Morgan et al reported disappearance of ascites in patients with ovarian cancer treated with intraperitoneal IdUrd (12). The pharmacologic activity of parent IPdR has not been firmly established, and it is primarily viewed as a prodrug to provide oral delivery of its active metabolite, IdUrd. IPdR was originally synthesized as an antiviral agent. Based upon its pyrimidinone structure and our unpublished data, IPdR might also serve as an inhibitor of cytidine deaminase. Previous reports indicated that plasma concentrations of IPdR in excess of $100 \mu M$ could be sustained for at least 6 hours following oral administration of IPdR in mice or rats (7, 8). In contrast, this clinical study found lower and more transient exposure for IPdR, which diminishes the potential for any direct pharmacologic activity from the parent compound.

Oral IPdR, as a convenient method of delivery of IdUrd, also offers the opportunity to reexamine previous diagnostic applications for IdUrd. As a probe for assessing the tumor proliferation rate, IPdR could be an alternative to intravenous bolus of bromodeoxyuridine (BUdR). BUdR is currently the most widely used measure of cellular proliferation in vitro (21), and the same techniques are applicable to IdUrd in vivo. Utilization of radioiodine isotopes, that have a long half-life (e.g., 4 days for ^{124}I), could provide a major logistical advantage as compared to the current use of 3′-deoxy-^{18}F-fluorothymidine (^{18}F-FLT) for imaging tumor proliferation, since ^{18}F-FLT has a half-life of only 110 minutes (22). Iodine isotopes of IdUrd have been shown to assess proliferation of tumors in *in vivo* models (23). However, release of free radioiodine creates background signal that obscures the imaging of DNA synthetic pathways. The secondary metabolite of IPdR, IUra, does not have established pharmacologic activity, but inhibits the enzyme dihydropyrimidine dehydrogenase. Inhibition of this enzyme could prevent the release of radioiodine from labeled IdUrd, overcoming the long-standing limitation to noninvasive measurement of tumor proliferation using radioiodine labeled IdUrd. In view of prior response heterogeneity and DNA incorporation, either an oral test dose of IPdR or PET imaging with ^{124}I could provide an enrichment strategy for patient selection.

This trial demonstrates the ability of a small, Phase 0 study to provide critical information for decision-making regarding future development of a drug. Adequate plasma levels of IdUrd were obtained to justify proceeding with a Phase I trial of oral IPdR in combination with radiation, and assessment of other diagnostic and therapeutic applications.

Acknowledgments

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Statement of Translational Relevance

Iododeoxyuridine (IdUrd), a halogenated nucleoside analog, produced clinical responses when administered as a radiosensitizer via continuous intravenous (c.i.v.) infusion over the course of radiation therapy. We conducted a Phase 0 trial of IPdR, an oral prodrug of IdUrd, in patients with advanced malignances to assess whether the oral route was a feasible alternative to c.i.v. infusion prior to embarking on large-scale clinical trials. Plasma concentrations of IPdR, IdUrd, and other metabolites were measured after a single oral dose of IPdR. Adequate plasma levels of IdUrd were obtained to justify proceeding with a Phase I trial of IPdR in combination with radiation. This trial demonstrates the ability of a small, Phase 0 study to provide critical information for decision-making regarding future development of a drug.
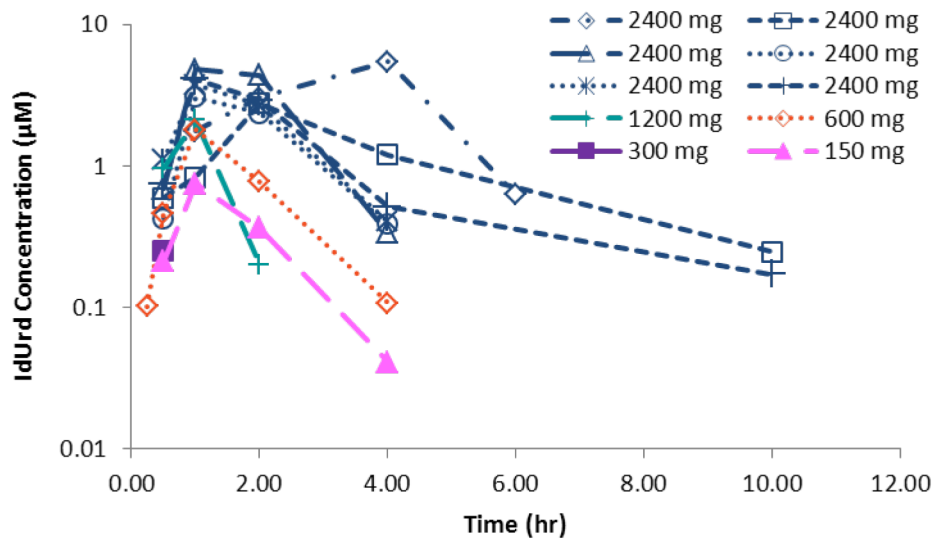
Figure 1.
Plasma exposures of the active metabolite IdUrd following a single dose of IPdR over the range of 150 to 2400 mg. Plasma concentrations remained above 1 µM for 3 to 4 hours and declined with a half-life of 1.5 hours.
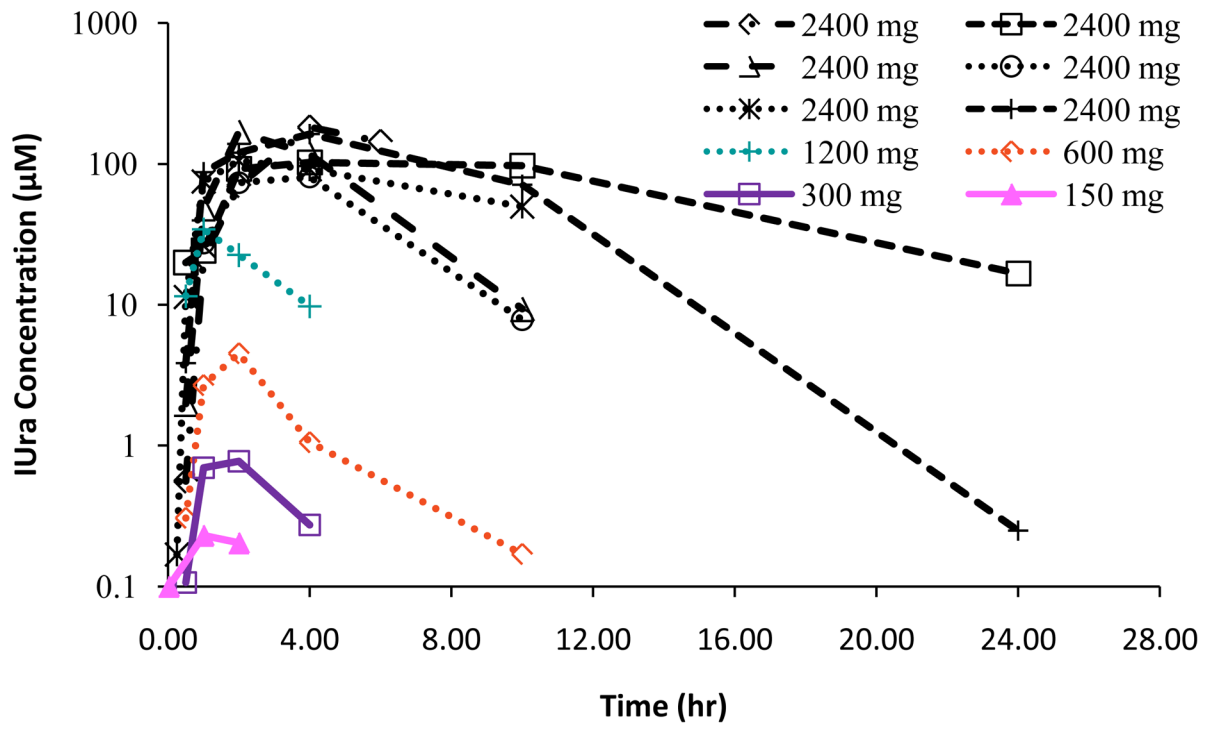
Figure 2.
Plasma exposures of the secondary metabolite, IUra, by dose level. Peak levels of IUra were reached 3.3 (± 1.0) hours post IPdR administration.

$$IPdR \longrightarrow IdUrd$$
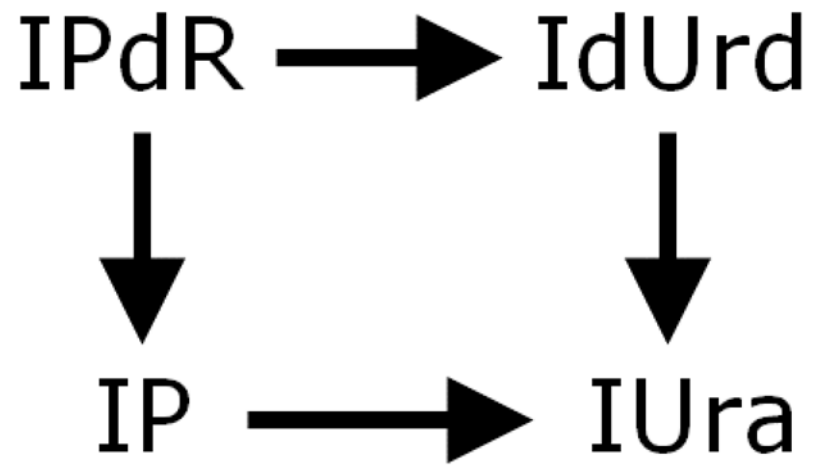
Figure 3.
Formation of metabolites of IPdR.

Table 1

Patient Demographics

Parameter	Value
No. of patients enrolled	10
No. enrolled by sex	
Female	2
Male	8
Age range, years	37–73
Diagnosis, No. of patients	
Adenoid cystic carcinoma	1
Bladder cancer	1
Breast cancer	1
Colorectal cancer	2
Hepatocellular carcinoma	1
Lymphoma	1
Neuroendocrine neoplasm	1
Thyroid	2

Table 2

Plasma Cmax and AUC values. Cmax units are µM; AUC units are µM-hr. One patient per dose from 150–1200 mg, and 6 patients at 2400mg. The patient at 300 mg did not have quantifiable concentrations of IPdR.

DOSE mg	IPdR AUC	IPdR Cmax	IdUrd AUC	IdUrd Cmax	IUra AUC	IUra Cmax
150	3.4	0.6	1.7	0.8	1.0	0.2
300	n.d.	n.d.	0.3	0.3	4.5	0.8
600	8.3	0.93	3.2	1.8	17.2	4.5
1200	0.7	0.95	4.7	2.1	102.7	34.2
2400	15.6	4.3	12.2	4.0	1057.8	133
SD	+/−18.8	+/−4.3	+/−3.9	+/−1.0	+/−483.5	+/−42.2