

Phase I Clinical and Pharmacological Study of Iododeoxyuridine and Bleomycin in Patients with Advanced Cancer¹

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ABSTRACT

Studies previously performed in our laboratory demonstrated synergistic cytotoxicity and DNA strand break formation in human tumor cells following exposure to a combination of bromodeoxyuridine and bleomycin. Synergy was evident when bromodeoxyuridine was administered prior to or simultaneously with bleomycin and occurred over a wide range of concentration ratios. We therefore undertook a phase I clinical trial of the combination of iododeoxyuridine (IdUrd) and bleomycin to determine the maximally tolerated dose of IdUrd that could be administered with a standard dose of bleomycin and to determine the toxicities of the combination. Eligible patients were those with advanced cancer refractory to standard therapy who had a performance status of 0-2, measurable or evaluable disease, and adequate organ function. IdUrd was administered as a 5-day continuous i.v. infusion beginning at a dose of 250 mg/m²/day with escalation in cohorts of 3-6 patients according to a modified Fibonacci scheme. Bleomycin was administered at a dose of 15 mg/m²/day as a continuous i.v. infusion during the last 3 days of the IdUrd infusion. Cycles of therapy were repeated every 28 days. Plasma levels of IdUrd and iodouracil were determined by high performance liquid chromatography. Thirty patients received a total of 79 cycles of IdUrd/bleomycin. Dose-limiting toxicity was bone marrow suppression. At the maximally tolerated IdUrd dose of 2780 mg/m²/day, the median neutrophil nadir after the first cycle of therapy was 805/ μ l and the median platelet nadir was 48,000/ μ l. Other toxic effects included mucositis, fatigue, nausea, diarrhea, fever, and skin toxicity. Plasma steady-state concentrations of IdUrd increased proportionally to administered IdUrd dose. IdUrd clearance varied from 0.253 liters/min/m² to 0.503 liters/min/m² and did not correlate with IdUrd dose. IdUrd dose and concentration correlated significantly with granulocyte and platelet nadirs, and a pharmacodynamic model for white blood cell count nadir could be defined by pretreatment white blood cell count, IdUrd dose, and gender. The recommended IdUrd dose for phase II testing of this combination is 2140 mg/m²/day. Phase II studies will be of particular interest in those diseases, such as carcinomas of the head, neck, and esophagus, where bleomycin has documented activity as a single agent.

INTRODUCTION

IdUrd³ is a halogenated thymidine analogue with established activity as a radiation-sensitizing agent. IdUrd alters many metabolic pathways within cells, including DNA synthesis and repair, but incorporation of IdUrd rather than thymidine into newly synthesized DNA is believed to be the primary mechanism by which radiosensitization occurs (1). The degree of radiosensitization depends on the extent of IdUrd incorporation into DNA, although the exact mechanism by which sensitization occurs is unknown (2). IdUrd also has intrinsic cytostatic and cytotoxic properties when used as a single agent (3).

One unexplored but potentially useful application of IdUrd may be its ability to potentiate the action of chemotherapeutic drugs as well as radiation. Russo *et al.* (4) reported enhancement of melphalan, Adriamycin, cisplatin, and neocarzinostatin cytotoxicity when Chinese hamster V79 cells were exposed to IdUrd prior to incubation with

these drugs. Other radiosensitizing agents, such as misonidazole, have also been shown to enhance the cytotoxic effects of some antineoplastic drugs (5).

Bleomycin is a commonly used anticancer drug effective in treatment of carcinomas of the head and neck, lymphomas, and germ cell tumors. The principal active component, bleomycin A2, has an aminoterminal tripeptide that binds to DNA, resulting in a DNA-bleomycin-Fe²⁺-O₂ complex. Subsequent reduction of oxygen to reactive species then damages the DNA causing single- and double-strand breaks that are believed to be the primary mechanism of cytotoxicity (6). Thus, bleomycin damages DNA in a way that resembles ionizing radiation, *i.e.*, by generation of highly reactive oxygen radicals within the cell.

Studies performed in our laboratory using the human head and neck carcinoma cell line SQ20B demonstrated synergistic cytotoxicity and DNA strand break formation by the combination of BrdUrd and bleomycin (7). Synergy was evident when BrdUrd was administered prior to or simultaneously with bleomycin and occurred over a wide range of concentration ratios. Alkaline elution of DNA from cells exposed to BrdUrd and bleomycin demonstrated greater single strand break formation than that produced by either drug alone. However, BrdUrd did not affect the rate of repair of bleomycin-induced single strand breaks or the formation of double strand breaks.

The clinical toxicities of the halogenated pyrimidines and bleomycin have been well-defined and do not appear to be overlapping, making these drugs excellent candidates for use in combination. Since preliminary clinical studies demonstrated a more favorable toxicity profile for IdUrd than BrdUrd, we selected IdUrd to combine with bleomycin in a phase I clinical trial. The specific objectives of the study were to define the maximally tolerated dose of IdUrd that could be administered with a fixed dose of bleomycin and to determine the toxicities of this combination.

PATIENTS AND METHODS

Patient Eligibility. Eligible patients were adults with a histologically documented solid tumor that was refractory to standard therapy or one for which no standard therapy was known to exist. All patients were required to have a performance status of 0-2 (Cancer and Leukemia Group B scale), a life expectancy of at least 4 weeks, measurable or evaluable disease, and no prior therapy with either IdUrd or bleomycin. Prior to entry on protocol, at least 4 weeks must have elapsed since the last chemotherapy dose (6 weeks if the prior therapy included mitomycin or a nitrosourea) or radiation treatment. Patients were also required to have adequate bone marrow, renal, and hepatic function manifest as a WBC \geq 3,500/ μ l, platelet count 100,000/ μ l, hemoglobin 10 g/dl, serum creatinine \leq 1.5 mg/dl, and total bilirubin \leq 1.5 mg/dl. Normal pulmonary function defined as a carbon monoxide diffusion capacity of at least 80% of predicted and a room air arterial oxygen partial pressure of at least 70 mm Hg were also required. All patients provided written informed consent in compliance with institutional and federal guidelines.

Treatment Plan. Patients were hospitalized for administration of each cycle of IdUrd plus bleomycin. IdUrd (NSC 39661) was provided by the National Cancer Institute in vials of 200 mg prepared as a white lyophilized powder with sodium hydroxide to adjust pH. The contents of each vial were reconstituted with sterile water for injection, and the total daily dose was then diluted in 1000 ml D5W and infused over 24 h. Bleomycin was obtained from commercial sources. The total daily dose was diluted in 0.9% sodium chloride and infused over 24 h. IdUrd was administered to patients as a 5-day (120 h) continuous i.v. infusion through one lumen of an indwelling double-lumen

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³ The abbreviations used are: BrdUrd, bromodeoxyuridine; IdUrd, iododeoxyuridine; IUra, iodouracil; HPLC, high performance liquid chromatography.

central venous catheter. Bleomycin was administered as a 3-day (72 h) continuous i.v. infusion during the last 3 days of the IdUrd infusion. The bleomycin dose was 15 mg/m²/day for all patients. Cycles of chemotherapy were administered every 28 days for a minimum of 2 cycles in the absence of dose-limiting toxicity or rapid tumor progression.

The starting dose of IdUrd was 250 mg/m²/day. This dose was selected based on prior clinical experience with IdUrd as a single agent (8). Doses were escalated according to a modified Fibonacci scheme in cohorts of at least 3 patients. There was no dose escalation in individual patients. At least 3 evaluable patients were entered at each dose level and observed for at least 4 weeks before entry of the next patient. If toxicity of grade 3 or greater was noted in any of the first 3 patients at a dose level, then 3 additional patients were enrolled at that dose level. The maximally tolerated dose was defined as that dose at which 3 of 6 patients experienced grade 3 toxicity or 2 of 6 patients experienced grade 4 toxicity. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria.

Study Parameters. Prior to treatment, all patients had a baseline medical history and physical examination as well as a complete blood count, platelet count, serum chemistries, pulmonary function studies including carbon monoxide diffusion capacity and arterial blood gases, chest X-ray, and appropriate scans or X-rays for evaluation of extent of disease. Patients were seen weekly in the clinic once treatment began. At each visit, a medical history was obtained, a physical examination was performed, and any toxicity was noted. In addition, a complete blood count and platelet count were determined. Serum chemistries, chest X-ray, and pulmonary function studies were repeated prior to the start of each cycle, and evaluation of extent of disease was performed after 2 cycles of therapy or sooner if clinically indicated.

Blood Sampling. Blood samples for IdUrd pharmacokinetic studies were obtained from an indwelling heparin lock prior to initiation of the IdUrd infusion and daily during the IdUrd infusion. Samples of 7–10 ml were collected in heparinized tubes on ice and centrifuged immediately at 3000 × g for 10 min. The plasma was then decanted and stored at –80°C in polyethylene tubes until analysis.

HPLC Analysis. A reverse phase HPLC assay was used for determination of plasma concentrations of IdUrd and iodouracil (9). Plasma samples were thawed to room temperature, and 100 µl of a solution of 0.1 M 5-bromouracil were added to 1 ml of plasma as an internal standard. Plasma proteins were precipitated by addition of 100 µl of 10% trichloroacetic acid and removed by centrifugation. The supernatant was then mixed with 8.0 ml of ethyl acetate and centrifuged again. The organic layer was decanted into a separate tube and dried under nitrogen at 37°C. The residue was reconstituted in 150 µl of 0.1 M NaOH, and 120 µl were injected onto the HPLC.

Injections were made onto a 3.9 mm x 300 mm 10 µBondapak C₁₈ column using a WISP 712 autosampler (Waters Assoc., Milford, MA). The mobile phase contained 25 mM acetic acid and acetonitrile (94:3). The flow rate was 2.0 ml/min for the first 7 min, 4 ml/min from min 7 to min 14, and then 2 ml/min from min 14 to min 17. This was achieved using a Waters model 510 pump and an NEC Powermate 396/25 computer with Maxima 820 software (Waters) for system control and data processing. UV detection was accomplished using a variable wavelength monitor 2141 (LKB-Pharmacia) set at 310 nm. Retention times of 5-bromouracil, 5-iodouracil, and IdUrd were 3.8, 5.4, and 10.6 min, respectively.

For each set of patient samples run, a calibration curve composed of plasma spiked with IdUrd was analyzed concurrently. Analysis of the calibration curves was performed using a weighted linear regression analysis by plotting the known concentration of IdUrd against the ratio of the IdUrd:bromouracil peak areas. Standard curves were constructed over the concentration range of 100 to 10,000 ng/ml. The intra-assay coefficient of variation was 7–8% and the interassay coefficient of variation was 5.6% over the linear range of the assay. The lower limit of quantitation was 100 ng/ml.

Pharmacokinetic Analysis. Total body clearance of IdUrd was calculated as:

$$Cl_{TB} = \frac{\text{Infusion Rate}}{C_{ss}}$$

the infusion rate/plasma IdUrd concentration at steady-state during the 120-h drug infusion.

Statistical Methods. The linear correlation of IdUrd dose to IdUrd concentration or clearance was assessed by Pearson's correlation coefficient.

Pharmacokinetic/pharmacodynamic models were constructed by stepwise multivariate regression for 3 measures of hematologic toxicity (natural log-transformed WBC, platelet, and absolute neutrophil count nadir counts). The covariate pool for these analyses consisted of IdUrd dose (mg/m²), total IdUrd dose (mg), IdUrd concentration, IdUrd clearance, age, gender (0 = male, 1 = female), performance status (0, 1, or 2), and natural log-transformed pretreatment WBC and platelet counts. The F statistic and coefficient of determination (r²) were used as measures of model aptness. Bias and precision were assessed by mean prediction error and root mean square error, respectively (10).

RESULTS

Thirty patients received a total of 79 cycles of IdUrd/bleomycin. The characteristics of the patients are shown in Table 1, and the doses administered are shown in Table 2. All but 2 patients were fully evaluable. One patient treated at an IdUrd dose of 2140 mg/m² withdrew consent midway through the first cycle of chemotherapy and refused to return for follow-up. One patient treated at an IdUrd dose of 2780 mg/m² died of congestive heart failure and pulmonary edema approximately 7 days after completing the initial course of chemotherapy. Although the patient had a prior history of cardiac disease, these events were considered possibly related to the chemotherapy treatment. Four patients had not previously received chemotherapy. The remaining 26 patients had received a median of 1 prior chemotherapy regimen; 13 of these patients had received only 5-fluorouracil-based chemotherapy, reflecting the preponderance of patients with colorectal cancer in this study.

Bone marrow toxicity was the primary and dose-limiting toxicity of this combination. As shown in Tables 3 and 4, there was minimal hematological toxicity at IdUrd doses below 1650 mg/m². At the maximally tolerated dose of 2780 mg/m², the median neutrophil nadir after the first cycle of therapy was 805/µl, and the median platelet nadir was 48,000/µl. Nadir blood counts occurred at a median of day 14 of the treatment cycle with complete recovery by day 28.

Other toxic effects observed in this study included fatigue, mild nausea, diarrhea, fever, and skin toxicity manifest as peeling, rash, palmar erythema, and cracked nails. These toxicities were observed at all IdUrd doses above 500 mg/m², and did not exceed grade 2 in severity. Dose-related mucositis was also noted to occur at IdUrd doses above 975 mg/m² (Table 5). At the maximally tolerated dose of 2780 mg/m², mucositis of grade 2 or 3 severity occurred in 3 of 5

Table 1 Patient characteristics

Total patients	30
Male	19
Female	11
Median yr of age (range)	59 (33–72)
Performance status (CALGB ^a)	
0	10
1	16
2	4
Prior therapy	
Chemotherapy	17
Chemotherapy and radiation	9
Radiation therapy	1
None	3
Diagnosis	
Colorectal	17
Sarcoma	3
Prostate	2
Melanoma	2
Renal	2
Cervix	1
Non-small cell lung	1
Gastric	1
Pancreas	1
Total	30

^a CALGB, Cancer and Leukemia Group B.

Table 2 Dose escalation scheme

IUdr entry dose (mg/m ²)	No. of patients	No. of cycles
250	4	8
500	3	6
750	3	10
975	3	8
1270	3	9
1650	3	14
2140	7	18
2780	4	6
Total	30	79

Table 3 Hematological toxicity, cycle 1

Dose (mg/m ²)	No. of patients	Median nadir (range)		
		WBC	ANC ^a	Platelets
250	4	4.3 (3.4–9.6)	2873 (2380–5664)	241 (201–356)
500	3	5.1 (1.8–6.2)	3348 (1008–3876)	189 (114–321)
750	3	5.0 (3.5–7.1)	3700 (1820–4828)	230 (104–294)
975	3	5.3 (2.4–8.7)	3392 (1128–4524)	263 (249–497)
1270	3	4.3 (2.0–4.6)	1935 (1080–2024)	203 (107–230)
1650	3	3.9 (3.4–4.2)	1394 (624–1848)	166 (153–207)
2140	7	3.0 (1.9–4.0)	904 (570–1560)	127 (109–193)
2780	3	2.8 (0.7–3.6)	805 (123–1224)	48 (14–115)

^a ANC, absolute neutrophil count.

Table 4 Hematological toxicity, all cycles

Dose (mg/m ²)	No. of patients	No. of cycles	Median nadir (range)		
			WBC	ANC ^a	Platelets
250	4	8	3.9 (3.2–9.6)	2450 (1792–5664)	213 (167–356)
500	3	6	4.9 (1.8–6.2)	3287 (1008–3876)	206 (114–321)
750	3	10	5.5 (2.7–7.1)	3405 (1820–5658)	209 (104–294)
975	3	8	5.5 (1.7–12.6)	3269 (646–8319)	242 (142–657)
1270	3	8	3.4 (2.0–4.6)	1764 (1080–2562)	118 (79–230)
1650	3	14	3.1 (2.4–4.2)	1310 (624–1908)	160 (80–238)
2140	7	18	2.9 (1.9–4.0)	1087 (570–2120)	96 (48–193)
2780	4	5	2.7 (0.7–3.6)	792 (123–1224)	52 (14–127)

^a ANC, absolute neutrophil count.

evaluable cycles. No significant pulmonary toxicity was observed during this study.

The IdUrd dose recommended for phase II studies in combination with bleomycin is 2140 mg/m²/day. At this dose level, all patients had neutrophil nadirs higher than 500 cells/μl and platelet nadirs higher than 100,000/μl during the first cycle of therapy.

Pharmacological Studies. Table 6 displays the steady-state concentrations of IdUrd and iodouracil and the clearance of IdUrd observed in this study. There was significant interpatient variability in IdUrd clearance with a coefficient of variation of 37%.

There was a strong linear relationship between administered IdUrd dose and plasma IdUrd concentration ($r = 0.88$; $P < 0.0001$) over the dosage range of this study. IdUrd clearance did not correlate with dose ($r = -0.32$; $P = 0.11$).

Plasma concentrations of IUra correlated significantly with both IdUrd dose ($r = 0.92$; $P < 0.0001$) and concentration ($r = 0.92$, $P < 0.0001$). Of particular interest was the relationship between the IUra/IdUrd concentration ratio and IdUrd dose (Table 6; Fig. 1). With increasing IdUrd dose this ratio progressively increased and appeared to plateau at IdUrd doses above 1270 mg/m².

The relationships between IdUrd dose and concentration, and hematological toxicity were also examined. In univariate analyses, IdUrd dose was significantly correlated with ln nadir WBC ($r = -0.54$; $P = 0.007$), ln nadir absolute neutrophil count ($r = -0.75$; $P < 0.0001$), and ln nadir platelet ($r = -0.67$; $P = 0.0004$). Significant correlations were also noted between nadir counts and IdUrd concentration. By stepwise multivariate regression, the best pharmacodynamic model for ln WBC nadir was defined by ln pretreatment WBC ($P = 0.04$), IdUrd dose ($P = 0.001$), and gender ($P = 0.02$): $\ln \text{WBC}_n$

(nadir white blood count) = $0.754 + 0.588 \ln \text{WBC}_p$ (pretreatment white blood count) – $0.000376 \text{ dose} - 0.453 \text{ gender}$. Female patients had worse myelosuppression.

The MPE ± SE of this model was $159 \pm 221 \text{ cells}/\mu\text{l}$, and the root mean square error was 1070 cells/μl, demonstrating that the model was unbiased and precise (Fig. 2).

DISCUSSION

Studies previously performed in our laboratory demonstrated that the combination of bromodeoxyuridine and bleomycin produced synergistic cytotoxicity and DNA strand break formation in human tumor cells (7). Initial clinical trials with both bromodeoxyuridine and IdUrd demonstrated bone marrow suppression to be the dose-limiting toxicity of these agents (11, 12). Since bleomycin is not toxic to the bone marrow when administered at conventional doses, we believed that a phase I trial combining a halogenated pyrimidine with bleomycin could be safely undertaken. IdUrd was used rather than bromodeoxyuridine because of its more favorable toxicity profile, particularly less skin toxicity (12).

The results of our phase I study demonstrate that the dose-limiting toxicity of the IdUrd/bleomycin combination is bone marrow suppression, both neutropenia and thrombocytopenia. Dose-related mucositis was also noted at IdUrd doses above 975 mg/m². Mild skin toxicity occurred in most patients treated at IdUrd doses above 500 mg/m² but was not clearly dose-related and was not dose-limiting. These toxic effects have all been reported to occur following administration of IdUrd as a single agent (8, 12). Although bleomycin can also cause skin toxicity, we found no evidence of synergistic toxicity to normal organs and, in particular, no evidence of enhanced bleomycin pulmonary toxicity. The recommended IdUrd dose for use in phase II studies of this combination is 2140 mg/m²/day. This dose is more than twice the maximally tolerated dose of 1000 mg/m²/day previously reported for IdUrd administered alone as a 14-day continuous infusion (12) and reflects the schedule-dependent cytotoxicity of this agent. With the shorter duration of exposure used in our study, it was possible to escalate the dose significantly.

Klecker *et al.* (9) studied the pharmacokinetics of IdUrd administered as a 14-day continuous i.v. infusion at doses ranging from 250 to 1200 mg/m²/day. IdUrd concentrations were found to reach steady-

Table 5 Mucositis, all cycles

Dose (mg/m ²)	No. of patients	No. of cycles	No. of cycles with grade:			
			1	2	3	4
250	4	8	1			
500	3	6				
750	3	10				
975	3	8	1			
1270	3	8	5			
1650	3	14	5	1		
2140	7	18	8		1	
2780	4	5	2	1	2	

Table 6 Pharmacokinetic parameters of IdUrd and iodouracil

Dose (mg/m ²)	No. of patients	C _{ss} ^a			
		IdUrd (μg/ml)	IUra (μg/ml)	Clearance IdUrd (L/min/m ²)	IUra:IdUrd molar ratio
250	2	0.712 ± 0.19 ^b	0.198 ± 0.077	0.253 ± 0.07	0.41 ± 0.05
500	3	0.776 ± 0.29	0.617 ± 0.396	0.503 ± 0.22	1.14 ± 0.38
750	2	1.71 ± 0.33	2.99 ± 0.474	0.310 ± 0.06	2.69 ± 0.93
975	3	1.55 ± 0.53	5.36 ± 2.80	0.469 ± 0.14	5.04 ± 1.47
1270	3	2.57 ± 0.73	14.12 ± 4.01	0.344 ± 0.09	8.32 ± 1.84
1650	2	3.89 ± 1.57	20.58 ± 2.26	0.321 ± 0.13	8.75 ± 4.38
2140	7	4.76 ± 1.53	18.45 ± 5.53	0.339 ± 0.10	6.40 ± 1.86
2780	4	8.09 ± 2.39	34.62 ± 5.80	0.254 ± 0.07	5.94 ± 0.95

^a C_{ss}, concentration at steady state.

^b Mean ± SD.

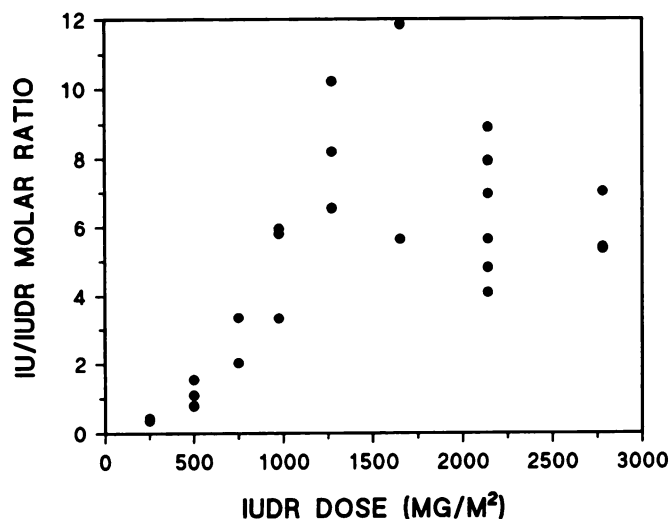


Fig. 1. Relationship between IUra:IdUrd molar ratio and IdUrd dose. Plasma concentrations of iodouracil and iododeoxyuridine were determined in patients receiving varying doses of IdUrd as a 5-day continuous i.v. infusion. IUUR, IdUrd.

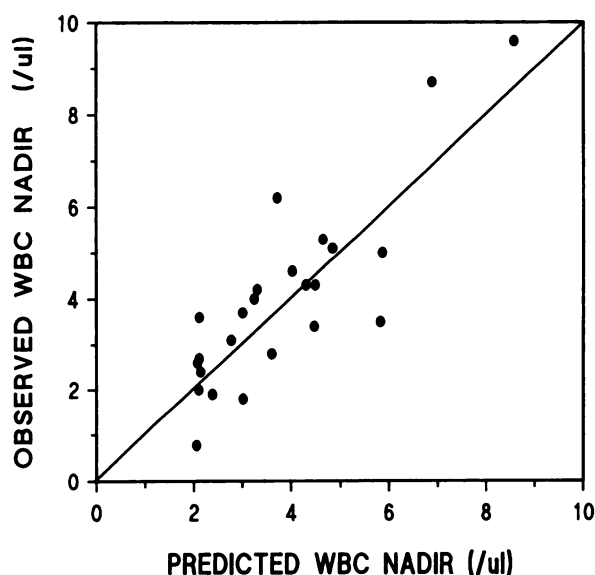


Fig. 2. Relationship between observed and predicted white blood count nadir in patients receiving 5-day continuous i.v. infusions of iododeoxyuridine ($r^2 = 0.60$; $P < 0.001$). The best pharmacodynamic model to estimate WBC nadir was $\ln WBC_n$ (nadir white blood cell count) = $0.754 + 0.588 \ln WBC_{pre}$ (pretreatment white blood cell count) - $0.000376 \text{ dose} - 0.453 \text{ gender}$.

state within 1 h of beginning the drug infusion, and plasma levels increased proportionally to the administered IdUrd dose. In our study, IdUrd was administered over a much wider range of doses, and significantly higher plasma concentrations were achieved. Even under these circumstances, however, the drug displayed linear pharmacokinetics.

Like Klecker *et al.* (9), we found that plasma concentrations of IUra exceeded those of IdUrd by approximately 5–8-fold. Indeed, at the highest IdUrd doses administered in our study, plasma IUra concentrations exceeded 100 $\mu\text{mol/liter}$ in most patients.

These levels are well above the K_m of 30 $\mu\text{mol/liter}$ that has been previously estimated for IUra clearance (9). As shown in Fig. 1 and Table 6, the IUra:IdUrd molar ratio increased progressively with increasing IdUrd dose and appeared to reach a plateau at IdUrd doses above 1270 mg/m^2 . The appearance of this plateau is consistent with

saturation of IUra clearance at plasma concentrations in excess of the reported K_m value.

Since bone marrow suppression was the dose-limiting toxicity in this phase I study, we examined the pharmacodynamic relationships between IdUrd dose and concentration and hematological toxicity. In univariate analyses, both IdUrd dose and concentration were significantly correlated with the natural log of the WBC, neutrophil, and platelet nadirs. By stepwise multivariate analysis, the best pharmacodynamic model for \ln WBC nadir was dependent on pretreatment white blood count, IdUrd dose, and gender. Once validated on an independent data set, this model, based on easily obtained clinical parameters, is potentially useful in guiding IdUrd dosing. Such a strategy might be important in view of studies previously reported by Belanger *et al.* (13), which demonstrated a significant inverse relationship between extent of incorporation of IdUrd into granulocyte DNA and the depth of the granulocyte and platelet nadir during IdUrd therapy. The apparent importance of gender in this model is difficult to explain. It is noteworthy, however, that gender has been reported to affect the pharmacodynamics of 6-mercaptopurine (14) as well.

Phase II studies of this combination chemotherapy program will be of particular interest in those diseases, such as carcinomas of the head and neck, esophagus, or uterine cervix, where bleomycin has documented activity as a single agent. For each of these diseases, concomitant administration of chemotherapy and radiation is being investigated (15) and the potential of employing IdUrd as both a chemosensitizing agent (with bleomycin) and as a radiosensitizing agent in a single treatment protocol is intriguing. Further clinical trials will be necessary to evaluate such a combined modality approach.

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