Phase I Trial of Hepatic Artery Infusion of 5-Iodo-2′-deoxyuridine and 5-Fluorouracil in Patients with Advanced Hepatic Malignancy: Biochemically Based Combination Chemotherapy


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ABSTRACT

Eighteen patients with hepatic metastases primarily from colorectal carcinoma were treated on a phase I protocol employing hepatic artery infusion (HAI) of 5-fluorouracil (FUra) and 5-iodo-2′-deoxyuridine (IdUrd) via an implantable infusion pump. Patients received a 14-day continuous HAI of 300 mg/day FUra. During days 8–14 of therapy, patients received IdUrd as a separate 3-h HAI daily × 7. Treatment cycles were repeated every 28 days. IdUrd was escalated from 0.1 to 2.86 mg/kg/day × 7.

Myelosuppression and stomatitis were mild and not dose limiting. Hepatotoxicity was dose limiting and similar to that reported for 5-fluoro-2′-deoxyuridine alone administered as a 14-day infusion every month. One patient developed a clinical picture consistent with sclerosing cholangitis and another had biopsy-proven cholestatics and triaditis. Catheter complications occurred in 7 of 18 patients.

Plasma concentrations of FUra during the 7-day continuous HAI of FUra alone were consistently either undetectable or very low (<0.1 µM). At level 3 (1.0 mg/kg/day IdUrd) and beyond, measurable plasma concentrations of FUra, iodouracil, and IdUrd were found at the end of the daily 3-h infusion of IdUrd. The maximum tolerated dose of IdUrd as administered in this trial is 2.2 mg/kg/day × 7 and the recommended starting dose for further clinical investigation is 1.7 mg/kg/day × 7.

INTRODUCTION

Hepatic metastases remain a common cause of morbidity and mortality in patients with colorectal carcinoma (1, 2). Therapeutic approaches have included surgical resection of isolated hepatic metastases (3) and systemic chemotherapy administered as a single modality (4) or in combination with irradiation (5). Recently, increased attention has focused on hepatic intraarterial infusion of chemotherapeutic agents (6–8). The latter approach is attractive since hepatic metastatic tumors derive their blood supply primarily from the hepatic arterial circulation (9, 10) and some agents are rapidly cleared by the liver, yielding a pharmacological advantage.

The pharmacokinetic properties of an agent which make it a potentially useful drug for regional administration include a short plasma half-life and high total body clearance. This permits the administration of higher concentrations of drug to tumors that are regionally confined with less likelihood of systemic toxicity (6). Similarly, substantial hepatic extraction of an agent will enhance the therapeutic index following hepatic artery infusion. The recent development of reliable and readily implantable infusion devices (e.g., Infusaid Pump; INFUSAID Corp., Norwood, MA) has greatly facilitated prolonged periods of drug administration.

The fluoropyrimidines are the drugs most widely employed in regional HAI therapy and generally are regarded as the most active agents in metastatic colorectal carcinoma. Of the other available halopyrimidines, IdUrd has considerable clinical experience and is useful as a radiosensitizer (11, 12). Suitable pharmacological properties of the fluoropyrimidines include their short plasma half-life, high total body clearance, and high hepatic extraction ratio (13, 15). FUra is metabolized to active moieties by a variety of mechanisms; the addition of deoxyribose by thymidine phosphorylase with subsequent formation ofFdUMP by thymidine kinase is a major pathway (13, 14). FdUMP binds to thymidylate synthetase, leading to inhibition of the de novo synthesis of dTMP and ultimately dTTP. The halopyrimidines FdUrd and IdUrd are converted to FdUMP and IdUMP in a single step by thymidine kinase. FdUrd exerts its cytotoxicity, like FUra, by blocking thymidylate synthetase upon conversion to FdUMP. IdUrd, on the other hand, is an analogue of thymidine and is directly incorporated into DNA upon phosphorylation to the trisphosphate nucleotide level (16, 17).

Catabolic pathways of IdUrd have therapeutic implications. IdUrd is rapidly metabolized to IUra by thymidine phosphorylase in the liver and peripheral circulation. Thymidylate synthetase dehalogenates IdUrd to dUMP, which is subsequently converted to dTMP (18, 19). Therefore, concomitant administration of fluoropyrimidines with IdUrd might be expected to enhance its cytotoxicity, by promoting increased incorporation of 5-ido-2′-deoxy-UTP into DNA as a result of decreased dTTP pools and by inhibiting the dehalogenation of IdUMP. Preclinical data confirm these observations both in vitro and in vivo (20–23). Limited clinical data regarding fluoropyrimidine and IdUrd combinations are available (24–31).

IdUrd has been shown to potentiate the cytotoxicity of FUra and FdUrd in vitro (21). Since diminished activity of thymidine kinase is one mechanism to account for cellular resistance to both IdUrd and FdUrd and since FUra does not depend on thymidine kinase for activation, FUra is an attractive drug to use in combination with IdUrd (32). FUra may also be advantageous because of possible therapeutic contributions made by effects on RNA metabolism (13, 14). Lastly, a limiting toxicity of HAI of FUra when administered on a 2-week on-2-week off schedule is biliary sclerosis (33–35). This toxicity has not been previously reported with HAI of FUra and might be circumvented by the use of the FUra and IdUrd combination.

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This report describes a phase I clinical trial employing HAI of FUra and IdUrd in the treatment of cancer patients with dominant hepatic metastases.

**MATERIALS AND METHODS**

**Patient Selection.** Patients with histologically documented malignancies and confirmed hepatic metastases were entered onto protocol between September 1984 and February 1987. Prior systemic or intrahepatic chemotherapy were not considered in determining eligibility for this trial. Signed informed consent was obtained from all patients in keeping with FDA and institutional guidelines. All patients had ECOG performance status of ≤2 (36), had a life expectancy of at least 12 weeks, had received no cytotoxic chemotherapy for 3 weeks prior to entry and no radiation therapy in the preceding 2 weeks, were free of active infection, and had adequate bone marrow (WBC count >4000/mm³, platelet count >100,000/mm³), liver bilirubin <2.0 mg/dl; SGOT and alkaline phosphatase <2 times normal), and renal (blood urea nitrogen <30 mg/dl; creatinine <2.0 mg/dl; normal urinalysis) functions.

**Pump Placement.** An INFUSAID pump (Model 400; INFUSAID Corp., Norwood, MA) was placed during exploratory laparotomy. The specifics of pump placement and function have been previously described (6–8). Preoperatively, all patients were evaluated by chest radiograph, computed tomography of the chest, abdomen, and pelvis, and angiography of the celiac, superior mesenteric, and hepatic arteries to evaluate extrahepatic disease and to define hepatic arterial circulation. At surgery, evaluation of all organs and sites of disease was completed. The presence of small peritoneal implants or resectable omental masses did not render patients ineligible for pump placement and study. Intraoperatively, the gastroduodenal artery was identified and dissected to its junction with the hepatic artery and branches to the pancreas and duodenum were ligated. The catheter was placed in the gastroduodenal artery such that its ostium lay within the gastroduodenal artery at its junction with the hepatic artery, and confirmation of catheter placement was undertaken with a radiolabeled albumin scan via injection through the side port of the pump. The pump was initially filled with 50 ml of sterile saline to which 10,000 units of heparin were added. The transbrachial artery catheterization technique for hepatic artery infusion was utilized for those patients who refused or were ineligible for pump implantation (37).

**Drug Administration.** FUra was administered at a dose of 300 mg/24 h for 14 days, via implantable pump or transbrachial artery catheter and Cormed pump; a 14-day rest period followed. This dose and schedule of FUra were chosen to accommodate the flow rate and volume of the pump and to permit subsequent correlation with the previously published experience for FdUrd. Treatment cycles were repeated every 28 days. The dose and rate of FUra administration remained constant throughout the trial. The first 12 patients received a 14-day infusion of FUra alone during the initial cycle of therapy, in order to assure that unusual sensitivity to intraarterial FUra therapy did not exist. In these 12 patients, starting with the second cycle of therapy and in all other patients during the first cycle, IdUrd was given during the second week (days 8–14) of FUra infusion. IdUrd was administered via the side port of the pump or by separate infusion pump through the transbrachial catheter as a 3-h infusion in 250 ml of 5% dextrose in water. The starting dose of IdUrd was 0.1 mg/kg/day x 7 (level 1) (see Table 2). For the last 14 days of each 28-day cycle, the pump was filled with 50 ml of heparinized saline. Patients were entered in groups of three at each IdUrd dose level. Two of three patients were observed for at least 3 weeks before starting new patients at an escalated level. Escalation to the next higher IdUrd dose was permitted in a patient who had received at least two cycles of combination HAI therapy without toxicity.

**Dose Modification.** If a patient had no evidence of myelosuppression or other toxicity over the 28-day treatment period, a second cycle could commence. Any patient who developed hepatotoxicity manifest by SGOT >2 times baseline or bilirubin >2.0 mg/dl was ineligible to receive further treatment unless hepatic dysfunction resolved. With documentation of rising serum hepatic enzyme content or bilirubin, treatment was discontinued and the pump was filled with heparinized saline. For patients developing clinical evidence of mild gastritis, antacids were administered. If pain worsened, ulcers were suspected and this required discontinuation of the drug infusion, initiation of heparinized saline infusion, and endoscopic evaluation as deemed clinically necessary.

**Patient Follow-up and Assessment.** A complete history, physical examination, and laboratory evaluation, including documentation of all measurable disease, was done within 48 h of entry onto protocol. During each cycle of therapy, weekly complete blood count with differential, platelet count, and serum chemistries were obtained. Documentation of pump function was obtained by recording the volume of infusate retrieved with weekly refills of the device.

**Disease assessment with appropriate radiological examination (abdominal computed tomography scan in most instances) was undertaken at approximately 2- to 3-month intervals. Radiolabel albumin hepatic perfusion scans were done at 3-month intervals to verify catheter placement. Toxicity and response criteria as defined by ECOG (36) were employed in this study. Hepatotoxicity was defined as follows: grade 1, SGOT or alkaline phosphate and/or bilirubin 1.5–2 times baseline (for entry, patients had to have bilirubin <2.0 mg/dl and SGOT and alkaline phosphatase <2 times normal); grade 2, SGOT or alkaline phosphate and/or bilirubin 2.1–5 times baseline; grade 3, SGOT or alkaline phosphate and/or bilirubin >5 times baseline and/or precoma; and grade 4, hepatic coma.

**Pharmacological Evaluation and Drug Assays.** Plasma samples were collected before treatment, on day 8 prior to the first IdUrd infusion, and at the end of the 3-h IdUrd infusion on selected days 8–14. Plasma concentrations of FUra, IdUrd, and IdUrd were measured simultaneously by high performance liquid chromatography, using a method similar to that of Stetson et al. (38), with 5-bromouracil as the internal standard. The limit of sensitivity of the assay was 0.1 μM in plasma for each drug. The within-day and between-day coefficient of variation for the assay was less than 10% at 0.5 μM for each drug and less than 5% at 2.0 μM for each drug.

**RESULTS**

**Patient Characteristics.** Eighteen patients were treated (Table 1). Patients had good performance status (15 with performance status of 0 or 1), the majority had received previous chemotherapy, and three patients had received prior HAI with FdUrd or FUra at higher doses. All but two patients had colorectal carcinoma.

Ten patients underwent exploratory laparotomy and placement of an implantable hepatic artery infusion pump. One patient underwent exploratory laparotomy and the hepatic artery was cannulated and connected to an Infusaport that was placed s.c. A Cormed pump was used to deliver drug therapy in this patient. Seven patients received their HAI therapy via a percutaneous transbrachial catheter.

Fourteen of 18 patients had measurable disease within the

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Sex (male/female)</th>
<th>12:6</th>
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<tbody>
<tr>
<td>Median age (range)</td>
<td>59 (28–76)</td>
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<tr>
<td>Performance status (ECOG)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Primary tumor</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>16</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Primary therapy</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>7</td>
</tr>
<tr>
<td>Systemic</td>
<td>8</td>
</tr>
<tr>
<td>HAI</td>
<td>3</td>
</tr>
<tr>
<td>Drug delivery system</td>
<td></td>
</tr>
<tr>
<td>INFUSAID pump</td>
<td>10</td>
</tr>
<tr>
<td>Hepatic artery Infusaport</td>
<td>1</td>
</tr>
<tr>
<td>Percutaneous transbrachial catheter</td>
<td>7</td>
</tr>
</tbody>
</table>
liver at the time of entry into study. Twelve patients had only intrahepatic metastases at the time of entry into study. In the other six patients, both intrahepatic and extrahepatic (retroperitoneal lymphadenopathy and/or peritoneal implants) disease was present.

Seventeen patients were evaluable for both toxicity and response. A single patient was excluded from this evaluation after receiving only 2 days of i.a. FUra alone; therapy was discontinued because of hepatic arterial thrombosis. Reductions in IdUrd dose were planned for myelosuppression and stomatitis but were not necessary during the conduct of this trial.

In these 17 patients, seventy-six 28-day courses of therapy were initiated, of which 71 were completed (Table 2). Five courses of therapy were not completed, three of which were due to catheter complications and the other two due to the development of progressive disease.

Toxicity. There was little toxicity in the 13 cycles of FUra administered alone in 12 patients. No myelosuppression was seen; two patients had grade 1 diarrhea, one patient had grade 1 fatigue, and one patient had a low grade (grade 2) fever, which was attributed to a concurrent viral illness.

Myelosuppression was mild. There were 11 episodes of grade 1 or grade 2 depression of hemoglobin. Leukopenia was a minor problem; one instance of grade 2 WBC suppression (nadir count, 2700/mm³) was seen. This episode of leukopenia occurred during the third cycle of treatment in a patient at level 6 and was associated with grade 2 hepatotoxicity. No thrombocytopenia was observed.

Gastrointestinal toxicity was also mild. A single episode of grade 1 stomatitis occurred in a patient during cycle 4 at level 6. This was the patient's second course at this level and this cycle was also complicated by grade 3 hepatotoxicity. One patient had grade 2 stomatitis during his fifth cycle of therapy at level 4. There was no other associated toxicity during this course. No other episodes of stomatitis were observed. Only five episodes of nausea and vomiting occurred and all were associated with concurrent hepatotoxicity (≥grade 2).

Eleven episodes of hepatotoxicity were observed in five patients, five grade 1, two grade 2, and four grade 3 (Table 3). Only two patients, both of whom had grade 1 hepatotoxicity, were entirely asymptomatic. The remaining nine episodes of hepatotoxicity occurred in three patients and were predominantly associated with complaints of grade 2 or worse anorexia and fatigue. Liver or right upper quadrant tenderness was noted on physical examination in two patients.

Of the four episodes of drug-related grade 3 hepatotoxicity, one occurred at level 5, two at level 6, and one at level 7. One patient experienced grade 3 hepatotoxicity after her fourth cycle of therapy, second course at level 6. Another patient developed grade 3 hepatotoxicity with her third cycle of therapy, first course at level 7 after receiving two prior courses at level 6. This patient experienced recurrent grade 3 hepatotoxicity at level 5 after 6 months of therapy. A third patient experienced grade 3 hepatotoxicity after the fourth cycle of therapy at level 6. A fourth patient developed hepatic dysfunction corresponding to grade 3 hepatotoxicity, which upon evaluation was proven to be due to progressive disease. We conclude that the maximum tolerated dose of IdUrd is 2.2 mg/kg/day × 7 when given as a 3-h infusion over the second week of a concurrent 14-day continuous HAI of 300 mg/day FUra.

Three patients were retreated after resolution of their hepatotoxicity. One patient received his 10th cycle (fourth course at level 4) without recurrent hepatotoxicity after having grade 1 hepatotoxicity with his ninth cycle. Two other patients had grade 1 hepatotoxicity with their first cycle of therapy at level 6. Hepatotoxicity in these two patients progressed to grade 2 in one patient retreated at the same level during the third cycle and, in the other, grade 3 upon escalation to level 7 during her third cycle.

The dose intensity of IdUrd, mg/kg/week, was calculated for the 17 evaluable patients for toxicity (Table 4). Courses of FUra alone were excluded in this determination. A single patient developed recurrent grade 3 hepatotoxicity but, because of a delay in treatment prior to this course, the dose intensity of IdUrd was calculated for the first episode. The median dose intensity of IdUrd was 1.37 mg/kg/week (range, 0–3.80) in the 12 patients who did not develop hepatotoxicity. These patients were treated for a median duration of 4 months (range, 1–9). In the five patients developing hepatotoxicity, the median dose intensity of IdUrd was 3.03 mg/kg/week (range, 1.56–4.24). These patients were treated for a median of 5 months (range, 3–9).

Two patients who experienced grade 3 hepatotoxicity are of particular interest. One patient, upon escalation to level 7 after two previous cycles at level 6, developed grade 3 hepatotoxicity, and, in the other, grade 3 upon escalation to level 7 during her third cycle.

### Table 2 Dose escalation

<table>
<thead>
<tr>
<th>Level</th>
<th>FUra (mg/day × 14)</th>
<th>IdUrd (mg/kg/day × 7)</th>
<th>No. of patients (new patients)</th>
<th>No. of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>0°</td>
<td>300</td>
<td>0.1</td>
<td>13 (10)</td>
<td>14</td>
</tr>
<tr>
<td>1</td>
<td>300</td>
<td>0.5</td>
<td>5 (3)</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>300</td>
<td>1.0</td>
<td>4 (4)</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>300</td>
<td>1.3</td>
<td>4 (1)</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>300</td>
<td>1.7</td>
<td>5 (4)</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>300</td>
<td>2.2</td>
<td>6 (3)</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>300</td>
<td>2.86</td>
<td>1 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>18</td>
<td>77</td>
</tr>
</tbody>
</table>

* The first 12 patients were treated with a first cycle of FUra alone and all went on to receive the combination except a single patient who developed a hepatic artery thrombosis. Another patient received FUra alone cycle later in her course because of a febrile illness. See text for details.

### Table 3 Hepatotoxicity by ECOG criteria

| Grade of hepatotoxicity by ECOG criteria (36) is given. See text for details. |
|-----------------|-----------------|-----------------|-----------------|
| Level           | No. of patients | No. of cycles  | % Total cycles  |
| 0–3             | 13              | 44              | 0               |
| 4               | 4               | 8               | 1               |
| 5               | 5               | 11              | 1               |
| 6               | 6               | 13              | 1               |
| 7               | 1               | 1               | 1               |
| Total           | 77              | 5               | 2               |

### Table 4 Dose intensity of IdUrd and incidence of hepatotoxicity

<table>
<thead>
<tr>
<th>IdUrd (mg/kg/week)</th>
<th>No hepatotoxicity</th>
<th>Hepatotoxicity (Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.56 (1)</td>
<td></td>
</tr>
<tr>
<td>0.38</td>
<td>2.98 (1)</td>
<td></td>
</tr>
<tr>
<td>0.38</td>
<td>3.03 (3)</td>
<td></td>
</tr>
<tr>
<td>0.75</td>
<td>3.42 (3)</td>
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</tr>
<tr>
<td>0.88</td>
<td>4.24 (3)</td>
<td></td>
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<tr>
<td>1.75</td>
<td>1.88</td>
<td></td>
</tr>
<tr>
<td>2.21</td>
<td>3.08</td>
<td></td>
</tr>
<tr>
<td>3.28</td>
<td>3.26</td>
<td></td>
</tr>
<tr>
<td>3.85</td>
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</tr>
<tr>
<td>Median Range</td>
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<tr>
<td></td>
<td>0–3.85</td>
<td>1.56–4.24</td>
</tr>
</tbody>
</table>
which resolved over a 4-month period. By week 10 of this
course of therapy, peak SGOT (124 units/liter), alkaline phos-
phatase (855 units/liter), and γ-glutamyltransferase (383 units/
liter) were attained. At no point was the patient jaundiced.
Because of rising liver enzymes an endoscopic retrograde cho-
langiopancreaticoduodenoscopy was performed during week 8.
This study demonstrated smooth narrowing of the bile duct just
distal to the bifurcation of the right and left hepatic ducts (Fig.
1) and was interpreted as being consistent with sclerosing cholangitis. This patient went on to receive an additional three
cycles of therapy at dose level 5 after recuperating from this
toxicity. The patient was severely jaundiced (peak bilirubin,
15.4 mg/dl) for the first time with the last cycle of therapy. She
recuperated from this toxicity and survived an additional 6.5
months after the last treatment with HAI drug therapy.

The other patient completed four cycles of therapy at level 6.
The first two cycles were associated with grade 1, the third
reversible grade 2, and the fourth grade 3 hepatotoxicity. Ab-
dominal computed tomography scan performed at the start of
the fourth cycle of therapy demonstrated at least one of three
intrahepatic lesions to be measurably smaller. At the conclusion
of the second week of cycle 4 of HAI with FUra and IdUrd, the
patient was noted to be jaundiced (bilirubin, 3.8 mg/dl) and to
have modest elevation of SCOT and alkaline phosphatase. He
became progressively jaundiced (peak serum bilirubin, 22.0 mg/
dl) and underwent exploratory laparatomy. Intraoperative find-
ings included: the prior radiographically visible hepatic métas-
tases in the right lobe of the liver were resolved; three needle
biopsies of this area were negative; segmental wedge resection
of two metastatic deposits of moderately well differentiated
adenocarcinoma in the left lobe that were in sites of disease
suspected radiographically, the hilum of the liver, was fibrotic;
and there was evidence of cholestasis and mild triaditis in the
biopsy specimen of the right lobe. This patient was previously
treated with HAI of FdUrd for 9 months and had transient
objective tumor regression prior to enrollment in this study. He
remains alive 1 year after discontinuing HAI protocol with
progressive disease, which has proven refractory to several
additional therapeutic interventions.

A total of seven catheter-related complications developed
during this trial. There were two episodes of angiographically
documented thrombosis of the hepatic artery, three episodes of
catheter tip migration, and two episodes of catheter tip fracture,
both of which occurred in patients with transbrachial devices.
No further sequelae developed from these complications after
appropriate intervention. There were no operative complica-
tions in this trial.

Pharmacokinetics. Systemic plasma concentrations of FUra
during the 7-day HAI of FUra alone, as measured on day 8
prior to the first IdUrd infusion, were consistently undetectable
or very low (≤0.1 μM). Commencing with level 3, 1.0 mg/kg/
day IdUrd, measurable systemic plasma concentrations of IUra
and IdUrd were attained at the end of each 3-h IdUrd infusion.
It was also noted that FUra plasma concentrations increased
from essentially nothing to about 0.5 μM in most cases.

Fig. 2 shows the mean plasma concentrations of FUra, IUra,
and IdUrd achieved at the end of the daily IdUrd infusions for
multiple courses in two patients. By day 9, the plasma concen-
trations of FUra, IUra, and IdUrd found at the end of each 3-
h IdUrd infusion were fairly constant. Table 5 summarizes the
pharmacokinetic data. Since not all patients were sampled every

![Fig. 1. Endoscopic retrograde cholangiopancreaticoduodenoscopy in patient
developing hepatotoxicity (see text for details). Arrow points out smooth narrow-
ing of bile duct just distal to bifurcation of right and left hepatic ducts consistent
with sclerosing cholangitis.](image_url)
day, the data are presented as the mean of the last peak sample drawn for each course, generally on days 12–14. The mean FUra plasma concentrations are consistent for levels 3–6, whereas the mean IUra and IdUrd concentrations increase with IdUrd dose. Plasma IUra concentrations are 2–3 times the corresponding IdUrd value. The data for the single course at level 7 is of interest. This is the course previously detailed which resulted in grade 3 hepatotoxicity. The FUra concentration is considerably higher than other courses, and the IUra level is 6 times the IdUrd concentration.

Response. Median duration of therapy was 4 months (range, 2 days to 10 months). A single patient had a partial remission, with greater than 50% reduction in measurable hepatic metastases on computed tomography of the abdomen. This patient had previously been treated with adjuvant FUra for a period of 1 year. This patient’s HAI drug therapy had to be discontinued after 4 months, because his hepatic artery catheter eroded into the duodenum and caused gastrointestinal bleeding. He developed extrahepatic progressive disease 5 months after being taken off study. Three patients had objective evidence of tumor regression which, however, was not sufficient to meet the criteria to establish a partial remission.

Seventeen patients were evaluable for analysis of site of progressive disease; the patient completing only 2 days of therapy was excluded. Intrahepatic disease progression developed in 11 patients and extrahepatic disease progression occurred in 6 patients.

DISCUSSION

This trial establishes that continuous HAI of combination FUra and IdUrd is feasible. Review of pharmacokinetic data demonstrates that, during the 7-day continuous HAI of 300 mg/day FUra, systemic plasma levels were either not detectable or were very low (<0.1 μM). This was expected because of the efficient extraction of FUra by the liver (15).

The systemic plasma levels of IdUrd reported here for FUra (Table 5) are substantially lower than plasma levels for peripheral venous infusions of IdUrd at comparable infusion rates. In two recent studies, plasma levels of IdUrd following infusions of 21 and 42 mg/m²/h were 1.1–1.3 and 2.4–2.7 μM, respectively (12, 27). For our dose levels of 1.7 mg/kg/day (about 21 mg/m²/h) and 2.2 mg/kg/day (about 28 mg/m²/h), we report systemic plasma levels of 0.42 and 0.81 μM, respectively. These differences are similar to those noted for FdUrd by Ensminger et al. (15).

Systemic plasma FUra levels were significantly increased with the concurrent administration of IdUrd. This may indicate perturbation of FUra metabolism, perhaps saturation of metabolic pathways for which IdUrd and FUra compete. This would result in the entry of FUra into the systemic circulation. The precise pharmacological and clinical significance of this observation is uncertain. In addition to the pharmacological modulation of FUra by IdUrd, presumably there is incorporation of IdUrd into DNA as well. Speth et al. (29) have demonstrated selective incorporation of IdUrd into hepatic tumor DNA when IdUrd is administered as a peripheral 3-day continuous infusion. Enhanced incorporation of IdUrd was observed when the same dose was administered via the hepatic artery (29).

Limiting toxicity in this trial was hepatic. Most other clinical manifestations of toxicity were associated with concurrent hepatotoxicity. The hepatotoxicity in this trial was akin to that seen with HAI of FdUrd (33–35). Patients developing hepatotoxicity received a greater dose intensity of IdUrd and tended to be treated for a longer period of time, when compared to patients who did not develop this toxicity. Grade 2 or greater hepatotoxicity was usually seen after two or three cycles of therapy (range, 1–6). Sclerosing cholangitis in one patient was documented and is a well recognized complication of HAI of FdUrd. Another patient was found to have histological evidence of extrahepatic biliary obstruction, cholestasis, and triaditis, which have also been described for HAI of FdUrd. Lastly, not unlike hepatotoxicity induced by FdUrd, hepatotoxicity in this trial tended to be cumulative and with interruption of therapy gradually resolved, permitting resumption of therapy at the same or reduced dose.

The spectrum of hepatotoxicity observed in this trial appears to be similar to that of HAI and FdUrd. It is noteworthy that previous studies have administered up to 1000–1200 mg/m²/day IdUrd i.v. for 14 days without dose-limiting hepatotoxicity (12, 27). The interconversion of FUra to FdUrd by thymidine is known (39, 40). IdUrd has not been shown to increase levels of thymidine when given as a single agent (12). It is possible that FdUrd may have been generated as a result of the coadministration of FUra and IdUrd. This would not be expected, however, because the plasma FUra levels in this trial were far below those reported for the interconversion of FUra to FdUrd by Au et al. (39).

Of note, hepatotoxicity was not invariably present in patients who demonstrated objective signs of tumor regression. The single patient with a partial remission had no complicating hepatotoxicity. In the three patients with evidence of minimal tumor regression, one patient had no hepatotoxicity and the other two had grade 1 and grade 3 hepatotoxicity, respectively. In addition, objective tumor regression occurred in a patient previously treated with HAI of FdUrd.

Catheter complications were similar to those reported in other trials (35, 41, 42). The implantable hepatic artery infusion pump was reliable and functioned well throughout the duration of this trial.

In summary, 18 patients with hepatic metastases, mostly from colorectal carcinoma, were treated in a phase I trial employing continuous HAI of FUra at 300 mg/day x 14 and an escalated dose of IdUrd as a bolus injection over the second week of therapy at monthly intervals. Hepatotoxicity was dose limiting. We would recommend a starting dose of 1.7 mg/kg/day x 7 for further clinical investigation. Although responses were seen, the precise clinical utility of this regimen remains to be determined, because the spectrum of hepatotoxicity experienced in this trial was not different than that seen with FdUrd administered on a similar schedule.

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HEPATIC ARTERY INFUSION OF IdUrd AND FuRa


Phase I Trial of Hepatic Artery Infusion of 5-Iodo-2’-deoxyuridine and 5-Fluorouracil in Patients with Advanced Hepatic Malignancy: Biochemically Based Combination Chemotherapy


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