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A Phase I Trial of Isolated Hepatic Perfusion (IHP) Using 5-FU and Oxaliplatin in Patients with Unresectable Isolated Liver Metastases from Colorectal Cancer

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Abstract

Background—Isolated hepatic perfusion (IHP) with melphalan is an established approach for patients with unresectable metastatic liver lesions. This study determined the safety and maximum tolerated dose (MTD) of 5-FU with oxaliplatin via IHP.

Methods—Standard 3 × 3 Phase I design. Subjects with unresectable isolated CRC liver metastases scheduled for HAI pump were eligible. IHP used fixed-dose oxaliplatin with escalating 5-FU doses. Toxicity (CTCAE v 4.0) and response (RECIST), progression-free survival, and overall survival (OS) were assessed. Systemic and IHP plasma PK of 5-FU, anabolites, and platinum were determined.

Results—All 12 patients had received 1 line of pre-IHP chemotherapy. There were 4 grade 3 serious adverse events (33.3 %) and 1 grade 4 event (8.3 %). Also, 2 dose-limiting toxicities occurred at DL2 at 300 mg/m², resulting in expansion of DL1 at 200 mg/m² 5-FU, the eventual MTD. At 6-month follow-up, 9 patients (82 %) demonstrated partial response, while 2 (18 %) exhibited stable disease. Also, 64 % of patients demonstrated a >50 % decrease in CEA. The 1- and 2-year OS probabilities were 90.9 and 71.6 %, respectively, with median follow-up of 24 months. IHP exposures (AUC_{0–60 min}) were 10.9 ± 4.5 µgPt h/mL, 49.3 ± 30.7 µg h/mL 5-FU (DL1), and 70.5 ± 35.5 µg h/mL 5-FU (DL2). Systemic exposure (AUC_{0–inf}) relative to IHP exposure was negligible for both platinum (1.1 ± 1.5 %) and 5-FU (0.09 ± 0.10 %).

Conclusions—The MTD for IHP was 200 mg/m² 5-FU with 40 mg/m² oxaliplatin. Systemic exposure to the agents was minimal during IHP. The response and survival observed warrants assessment in a larger phase II trial.

Regional therapy in the form of hepatic arterial infusion (HAI) with FUDR as a sole first-line therapy for unresectable colorectal liver metastases has been extensively studied in numerous prospective clinical trials.^{1–5} These trials have demonstrated increased response rates, but definitive proof of improved overall survival has been lacking. A more recent randomized trial demonstrated survival with the addition of HAI FUDR to systemic chemotherapy, implicating the need to combine regional and systemic therapy.⁶

Isolated hepatic perfusion (IHP) is a proven regional chemotherapeutic approach for metastatic unresectable colorectal cancer (CRC).^{1,2,7} In CRC, trials using IHP with melphalan alone demonstrate that its combination with other therapy, in the form of either HAI (FUDR) or systemic chemotherapy, is associated with significant progression-free survival, duration of response, and overall survival.^{8–12}

We recently reported a phase I dose-escalation trial of hyperthermic IHP with oxaliplatin in patients with unresectable metastatic CRC scheduled to undergo placement of an HAI pump. At the maximum tolerated dose of 40 mg/m², only minor transient liver dysfunction was observed and overall response rate to combined IHP and HAI therapy was 66 %.^{13,14} Given these previous findings and significant preclinical work suggesting synergy between 5-FU and oxaliplatin, we sought to perform a similar study using a combination of escalating doses of 5-FU and fixed-dose oxaliplatin.^{15,16} Our primary objective was to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of 5-FU delivered with 40 mg/m² of oxaliplatin in the setting of IHP. Our secondary objectives were to determine response rate, duration of response, and survival after isolated hepatic perfusion with 5-FU and oxaliplatin. Additionally, we sought to determine the pharmacokinetic and tissue absorption (liver vs. tumor) of oxaliplatin and 5-FU delivered in the IHP setting.

PATIENTS AND METHODS

Eligibility

Subjects who had isolated unresectable liver metastases from CRC and were scheduled for HAI with FUDR were eligible for enrollment in this phase I trial. Limited resectable extrahepatic disease was acceptable if the liver was felt to be the dominant site of life-threatening disease. Additional important inclusion criteria included: adequate hepatic function as evidenced by bilirubin <2.0 mg/dL, PT <2 s greater than the upper limit of normal, serum total bilirubin <1.5 mg/dL. Alkaline phosphatase <5× the upper limit of normal (ULN), SGOT/SGPT <5× the ULN, and patients with significant history of underlying hepatic disease were excluded.

The study was approved as an exempt study by the U.S. Food and Drug Administration. It was reviewed and approved by The University of Pittsburgh Institutional Review Board (IRB), and the University of Pittsburgh Cancer Institute Protocol Review Committee. The trial was registered with the NCI at Clinical trials.gov, protocol no. NCT00557557. All patients read and signed consent prior to enrollment in the protocol. Monitoring was performed by the UPCI independent data safety monitoring board and the principal investigators.

IHP Procedure and 5-FU Dosing Schema

IHP was administered as previously described.^{8,14} The starting dose of 5-FU administered via isolated hepatic perfusion in combination with 40 mg/m² oxaliplatin was based on the starting doses of previous IHP trials with 5-FU, with initial dose of 200 mg/m².^{1,2} Ideal weight was used for the dosing of 5-FU and oxaliplatin. Standard 3 × 3 dose escalation design was used. Escalation to the higher dose occurred if no DLT was observed at the lower dose. All patients in a cohort were observed for at least 6 weeks after drug administration for evidence of DLT before beginning accrual to the next higher dose level.

Definition of DLT

Because IHP is administered in the context of a major operative procedure, it is important to distinguish the contribution of the surgical procedure itself from that related to treatment. Therefore, only grade III or IV major organ toxicity (excluding the liver) related to the

research intervention and irreversible within 48 h of the IHP was scored as a treatment-related DLT. During IHP, the liver is manipulated and perfused with a hyperthermic and slightly acidotic blood-primed saline solution. Because of these contributing factors, hepatic transaminase and bilirubin levels typically are very high for approximately 2–3 days and then return toward normal within 7 days. Therefore, liver toxicities were graded according to the following criteria: If serum SGOT and SGPT did not decrease and were greater than 10× the upper normal limit (i.e., >410 U/L for ALT and >340 U/L for AST) at 14 days after IHP, this was graded as a DLT. DLT for hyperbilirubinemia was scored in 2 fashions: (1) Any hyperbilirubinemia in the first 6 weeks associated with clinical signs of veno-occlusive disease (VOD) was considered a DLT. (The clinical diagnosis of VOD is made based upon fluid retention, weight gain >2–5 % baseline, progressive hyperbilirubinemia, and ascites.) Pathological confirmation of VOD is made by the presence of occluded hepatic venules sinusoidal fibrosis and hepatocyte necrosis. (2) Grade III or IV hyperbilirubinemia that did not resolve by 6 weeks after the IHP was also considered a DLT.

Systemic and regional toxicity were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE v 4.0).

Response

All patients underwent a CT scan of the liver to use as a baseline for assessing response within 3 weeks of the procedure. Following the procedure, patients were followed every 3 months with CT scan and CEA level. Responses were assessed by RECIST criteria on the second interval CT scan (5–6 months post-IHP).

Pharmacokinetic Analysis

Both afferent and efferent perfusate was sampled before and 5, 15, 30, 45, and 60 min after addition of 5-FU and oxaliplatin to the isolated hepatic circulation to characterize the hepatic exposure to these drugs and metabolites. To document incomplete isolation, and/or spillage of perfusate resulting in systemic drug exposure, peripheral blood plasma was obtained before and 5, 15, 30, 45, 60, 75, 90, and 120 min after the start of perfusion. Blood and perfusate samples were transferred to heparinized vacutainer tubes, immediately placed on ice, and centrifuged at $1,000\times g$ for 10 min. The resulting supernatants were stored at -80°C , until quantitative analysis. Total platinum (Tot) represents the platinum species present, in whichever form, including platinum reacted and bound to macromolecules. Ultrafilterable platinum (UF) represents low molecular weight platinum and contains platinum species that are still reactive with nucleophiles such as DNA and proteins. Ultrafiltrates of perfusate and plasma were prepared by placing 1 mL of each sample into an Amicon Centrifree micropartition device (Amicon Division, W.R. Grace, Beverly, MA) and then centrifuging those devices at $2,000\times g$ for 20 min at 4°C . Concentrations of 5-FU were quantitated with an LC–MS/MS assay previously developed in our laboratory and validated according to the most recent FDA guidelines.¹⁷ Concentrations of 5-FdUrd and 5-FUrd were quantitated with an LC–MS/MS assay as previously described.¹⁸ Total platinum concentrations in plasma, perfusate, and ultrafilterable platinum in their respective ultrafiltrates were assessed with a Perkin-Elmer model 1100 flameless atomic absorption spectrometer (Perkin-Elmer, Norwalk, CT) as previously described.¹⁹ Platinum concentrations were determined by comparison with a standard curve performed in an appropriate matrix and on the same day as the assay. Plasma pharmacokinetic parameters were extracted from the data by noncompartmental methods with PK Solutions 2.0 (Summit Research Services, Montrose, CO).

Statistical Analysis

Response was described, and overall survival was assessed. Overall survival was defined as the time from date of diagnosis until date of death, and survival probabilities were estimated using the Kaplan–Meier method. Patients who did not die were censored on their date of last follow-up. Analyses were performed using SAS 9.3(Cary, NC). Systemic and IHP plasma pharmacokinetics of 5-FU and anabolites, and total and free platinum were determined by validated LC–MS/MS and atomic absorption spectrophotometry assays.

RESULTS

Patient Characteristics

Between August 2011 and March 2012, 12 subjects underwent treatment (Table 1). There were 9 women (75 %), median age of 55.5 years, and clinical risk score (CRS) of 3.²⁰ All 12 patients received at least 1 line of pre-IHP systemic chemotherapy. Median percentage of replaced liver by tumor was 42.5 % with a median number of 10.5 metastatic lesions, indicating heavy tumor burden prior to IHP therapy. All 12 patients underwent IHP with oxaliplatin at 40 mg/m²; 5-FU was dose escalated beginning at 200 mg/m² (Table 2).

Adverse Events/Toxicities

There were 4 grade 3 serious adverse events (SAEs) (33.3 %) and 1 grade 4 event (8.3 %) (Table 2). These SAEs included hemorrhage requiring reoperation (grade 3), pleural effusion (grade 3), hematoma, hyperbilirubinemia (grade 3), and anastomotic dehiscence (grade 4). Also, dose-limiting toxicities occurred in the second dose cohort of 300 mg/m². One of these patients had significant hyperbilirubinemia, and the second patient developed significant ascites secondary to hepatic failure. Dose escalation was therefore terminated, and an additional 3 subjects were treated at 200 mg/m² 5-FU. There was 1 DLT in the dose de-escalating phase of 200 mg/m².

As expected, all 12 patients had evidence of transient liver injury manifested by rises in AST and ALT. In 10 of the 12 patients, liver enzymes returned to baseline by 2 weeks postoperatively.

Response and Survival

A total of 9 patients (82 %) demonstrated a partial response defined by RECIST criteria, while 2 (18 %) exhibited stable disease (Table 2). Also, 64 % of subjects demonstrated a >50 % decrease in CEA level by 6-month follow-up. Of the 7 responders, 3 (42 %) had complete normalization of their CEA levels during their respective follow-up periods. Also, 1 patient who initially had unresectable bilobar hepatic disease went on to undergo liver resection approximately 1 year following IHP therapy. Of the 12 patients, 11 had completed at least 6 months of evaluation follow-up at time of manuscript preparation evaluation of survival. Of these 11 patients, 10 received FUDR, with median number of 2 cycles and median time to HAI therapy of 5 weeks. Patients' responses are secondary to the combined IHP/HAI treatment and cannot be stated to be solely due to IHP since initiation of HAI therapy occurred prior to all patients' second interval CT scans (Fig. 1). The 1- and 2-year overall survival probabilities were 90.9 % (95 % CI 50.5–98.7 %) and 71.6 % (95 % CI 35.0–89.9 %) respectively, with median follow-up of 24 months.

Pharmacokinetics

Pharmacokinetic studies were successfully performed in 11 patients. Afferent and efferent concentrations were identical, and only afferent is reported here. Concentrations of total and ultrafilterable platinum in perfusate decreased with time in a nearly parallel fashion as

expected from a relatively nonreactive platinating agent such as oxaliplatin (Fig. 2a). Free platinum represented approximately 83 % of total platinum. Similarly, concentrations of 5-FU also decreased with time (Fig. 2b), and the exposure of 5-FU was dose-proportional (Table 3). Concentrations of the 5-FU anabolites 5-FUrd and 5-FdUrd were lower than concentrations of parent 5-FU concentrations (Fig. 2c, d), see also Table 3. 5-FUrd was approximately 20-fold more abundant than 5-FdUrd, and the ratio of both metabolites relative to parent 5-FU approximately doubled with increasing the dose by 50 %. Systemic exposure (AUC_{0-inf}) relative to IHP exposure was negligible for both total platinum (1.1 %) and 5-FU (0.12 %).

DISCUSSION

We established the MTD of 5-FU to be 200 mg/m² when given in combination with oxaliplatin (40 mg/m²). Similar to our previous IHP studies, dose-limiting toxicity was in the form of irreversible hepatic injury. It is interesting to note that our MTD was within the first dose cohort and was significantly lower than the previously reported MTD for 5-FU alone. Aigner et al.²¹ reported safe doses of 5-FU between 700 and 1,100 mg delivered with hyperthermia as an hour-long perfusion in 32 patients. Schwemmle et al.²² reported 5-FU (300–1,250 mg) delivered in combination with mitomycin C as an isolated hepatic perfusion in 50 patients. This discrepancy between our MTD and the doses previously given likely represent temporal differences in the studies. The 2 previous studies had been performed at a time prior to modern systemic regimens, which may have led to worse hepatic dysfunction at baseline for many of our subjects.²³ All subjects in the current study had received at least 1 line of systemic chemotherapy (oxaliplatin and/or irinotecan + 5-FU based regimen) prior to IHP. It is possible that if IHP/FUDR therapy were moved earlier in the treatment algorithm that higher doses may be tolerated. However, the realities of current practice patterns will not likely allow for this evaluation and the current recommended dose is tolerated in a majority of heavily pretreated subjects.

The increasing ratio of metabolites to 5-FU with increasing dose suggests a saturation of the catabolic pathway of 5-FU in favor of the anabolic pathways generating 5-FUrd and 5-FdUrd. The absolute exposure of 5-FUrd almost tripled upon increasing 5-FU dose by 50 %. This nonlinear dose-dependent increase in 5-FU metabolite exposure may be part of the reason more toxicities (DLTs) occur at higher doses of 5-FU. The pharmacokinetics also demonstrates that a 1-h perfusion is an appropriate time frame from a pharmacological perspective. Because of significant 5-FU metabolism after 1 h, a longer perfusion would not be associated with a relevant increase in drug exposure. Likewise, concentrations of ultrafilterable platinum had decreased significantly after 1 h. A shorter perfusion would significantly reduce exposure to ultrafilterable platinum, while a longer perfusion would likely not increase exposure significantly. Given the increased risk associated with longer surgical procedures, limiting the perfusion to 1 h is deemed appropriate. The pharmacokinetic data also confirmed minimal systemic exposure to the 2 agents and to their breakdown products. These results confirm that by implementing the isolated perfusion approach, high target organ exposure to the agent of choice can be achieved without significant systemic exposure.

Despite the limitations of evaluating efficacy endpoints in a phase 1 trial, we consider the response rate of 82 % as quite encouraging for this pretreated cohort of patients. Recent studies examining the combination of HAI with FUDR and systemic chemotherapy for colorectal metastases have reported response rates from 74 to 100 %.^{24–29} Median survival in these studies ranged from 20 to 51 months.^{28,29} In a recent report examining the combination of systemic chemotherapy and HAI therapy, Kemeny et al. reported median and 2-year survival from the time of HAI pump placement to be 32 months and 63 %,

respectively, in those patients without extrahepatic disease and 16 months and 33 %, respectively, in those patients with extrahepatic disease. In the current study of IHP, HAI and systemic chemotherapy 1- and 2-year survival probabilities were 91 and 72 %, respectively, with median follow-up of 24 months. One patient who initially had unresectable bilobar hepatic disease went on to undergo liver resection approximately 1 year following IHP therapy. Our encouraging results suggest that the addition of IHP to HAI and systemic chemotherapy may further improve local control rates and potentially offer a survival benefit. However, larger trials will be necessary to fully understand the potential efficacy of this approach for patients with unresectable CLRM.³⁰

In conclusion, the results of this phase 1 study support further investigation of IHP into the overall treatment algorithm of patients with unresectable colorectal metastases.³¹ The preponderance of data supporting the enhanced response rates of locoregional therapy and the emerging evidence supporting improved survival when combined with modern systemic regimens suggests a rethinking of predominant current approach of systemic chemotherapy until exhaustion in this population.^{32–39}

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FIG. 1.
CT pre-IHP and post-IHP (6 months) treatment

FIG. 2. Mean ($\pm$ SD) total and ultrafilterable platinum (**a**), and dose level 1 and dose level 2 5-FU (**b**), 5-FUrd (**c**), and 5-FdUrd (**d**) concentrations in isolated hepatic perfusate

TABLE 1

Patient characteristics

Number of patients (<i>n</i>)	12
Median age, years (range)	55.5 (32–63)
Ratio, females:males	9:3
Clinical risk score, median (range)	3 (1–4)
No. of metastatic lesions, median (range)	10.5 (5–102)
Liver replaced by tumor, %, median (range)	42.5 % (25–80 %)
Prior chemotherapy, <i>n</i> (%)	12 (100 %)
Folfox/folfiri, <i>n</i> (%)	10 (83 %)
No. of cycles FUDR received, median (range)	5 (0–8)

Adverse events, toxicities, and response

TABLE 2

Patient No.	5FU dose (mg/m ²)	Oxaliplatin dose (mg/m ²)	DLT	SAE (grade)	Type of SAE	Response
1	200	40	No	No		PR
2	200	40	No	No		PR
3	200	40	No	No		PR
4	300	40	No	No		PR
5	300	40	Yes	Yes (3)	Hyperbilirubinemia, hemorrhage	PR
6	300	40	No	No		SD
7	300	40	No	Yes (3)	Pleural effusion	PR
8	300	40	No	No		PR
9	300	40	Yes	Yes (3)	Hematoma, ascites	PR
10	200	40	Yes	Yes (3)	Thrombocytopenia, hemorrhage, pleural effusion	SD
11	200	40	No	No		PR
12	200	40	No	Yes (4)	Anastomotic dehiscence	PR ^a

DLT dose-limiting toxicity, SAE serious adverse event, PR partial response, SD stable disease

^a At 3-month follow-up

TABLE 3

Pharmacokinetic parameters of platinum and 5-FU and metabolites in hepatic perfusate and peripheral blood plasma

	AUC _{0-t} (µg h/mL)	C _{max} (µg/mL)	T _{max} (min)	C _{max} -ratio Pt _{tot} Aff (%)
DL1 + 2				
Pt _{uf}	10.6 (4.3)	14.5 (5.4)	–	–
Pt _{tot}	12.8 (4.6)	17.0 (5.4)	–	–
Pt _{tot_sys}	0.28 (0.34)	0.18 (0.09)	123 (42)	1.1 (0.8)
	AUC _{0-t} (µg h/mL)	C _{max} (µg/mL)	T _{max} (min)	AUC-ratio to 5FU Aff
DL1				
5FU				100
5FUrd	1.79 (1.52)	2.79 (2.11)	16 (9)	3.4 (2.6)
5FdUrd	0.076 (0.059)	0.194 (0.094)	16 (9)	0.15 (0.12)
5FU _{sys}	0.05 (0.06)	0.039 (0.012)	14 (10)	0.12 (0.12)
DL2				
5FU	70.5 (35.3)	144 (48)	–	100
5FUrd	4.88 (3.09)	8.60 (3.91)	22 (12)	6.5 (1.4)
5FdUrd	0.17 (0.04)	0.383 (0.91)	19 (15)	0.29 (0.12)
5FU _{sys}	0.05 (0.03)	0.056 (0.023)	13 (5)	0.05 (0.04)

DL dose level