A Phase I Study of Hyperthermic Isolated Hepatic Perfusion with Oxaliplatin in the Treatment of Unresectable Liver Metastases from Colorectal Cancer

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ABSTRACT Isolated hepatic perfusion (IHP) is a proven approach for regional delivery of chemotherapy in patients with unresectable primary and metastatic tumors of the liver. Most trials of IHP have utilized melphalan as the active drug in the perfusate. We performed a phase I trial to evaluate the efficacy, safety, and maximum tolerated dose (MTD) of oxaliplatin delivered by hyperthermic isolated hepatic perfusion. A phase I dose-escalation trial of hyperthermic IHP with oxaliplatin in patients with unresectable metastatic colorectal cancer scheduled to undergo placement of a hepatic arterial infusion (HAI) pump was carried out. Thirteen patients were enrolled between November 2003 and September 2006. Dose-limiting venoocclusive disease was observed at 60 mg/m². At the MTD of 40 mg/m² only minor transient liver dysfunction was observed. Ultrafilterable platinum area under the curve and maximum concentration delivered by IHP increased nonlinearly with dose as did platinum concentrations in liver biopsies obtained at the end of the 60 min IHP. Seventy-seven percent of patients had a >50% decrease in serum carcinoembryonic antigen (CEA) after IHP. The overall response rate to the combined IHP and HAI therapy was 66%. One patient had a durable complete response (>4 years). We conclude that hyperthermic IHP with oxaliplatin was safe and feasible at a dose of 40 mg/m². The ability to obtain complete vascular isolation with open IHP was confirmed. The response rate in this small phase I study was encouraging.

Cancer of the colon and rectum is the third most frequent site of cancer in the USA, and accounts for approximately 150,000 new cases annually. Hepatic metastases as the sole or dominant site of life-limiting disease occur in approximately 20–50% of patients with colorectal cancer. Median survival of patients with untreated colorectal cancer hepatic metastases ranges from 4 to 12 months. Complete surgical resection of isolated colorectal cancer hepatic metastases results in 5-year overall survival rates between 32% and 58%. Unfortunately, only 10–20% of patients with colorectal metastases to the liver are eligible for resection. Systemic chemotherapy is the predominant treatment for patients with unresectable liver metastases from colorectal cancer. Novel regimens that combine multiple cytotoxic agents such as 5-fluorouracil (5-FU), oxaliplatin, and irinotecan, in combination with agents such as bevacizumab and cetuximab, are associated with response rates approaching 70% and median survival approaching 2 years. Despite these more effective regimens, the majority of patients with unresectable liver metastases eventually succumb to their disease, therefore durability and completeness of response remain major unsolved issues. Several recent retrospective studies have suggested that aggressive combination of systemic chemotherapy and subsequent surgical resection of colorectal cancer hepatic...
Eligibility Criteria

Patients and Methods

oxaliplatin pharmacokinetics and response rate. Hyperthermic IHP. Secondary endpoints were evaluation of limiting toxicity (DLT) of oxaliplatin when delivered via hyperthermia, would make it a better drug than melphalan in vitro findings suggesting that its efficacy is improved by cacy of oxaliplatin against colorectal cancer, and the in regimen in the perfusate. We hypothesized that the effi-
cancer.5,20 The current limitations to more widespread application of IHP include the technically demanding nature of the procedure and the need for more effective chemotherapeutic agents for inclusion in the perfusate. To address these issues, we recently developed a novel combined percutaneous and open technique for IHP that decreases operative time and complexity. In addition, we examined the safety and efficacy of novel chemotherapy regimens in the perfusate. We hypothesized that the efficacy of oxaliplatin against colorectal cancer, and the in vitro findings suggesting that its efficacy is improved by hyperthermia, would make it a better drug than melphalan for use in IHP. We report here the results of a phase I study to determine the maximum tolerated dose (MTD) and do- limiting toxicity (DLT) of oxaliplatin when delivered via hyperthermic IHP. Secondary endpoints were evaluation of oxaliplatin pharmacokinetics and response rate.

Patients and Methods

Eligibility Criteria

Patients who had isolated unresectable liver metastases from colorectal cancer and were scheduled for HAI with 5-fluorodeoxyuridine (FUDR) were eligible for enrollment. Patients were required to have histologically or cytologi- cally proven measurable metastatic colorectal cancer that was limited to the parenchyma of the liver, although limited resectable extrahepatic disease was acceptable. Unresectable disease was defined as multiple bilobar tumors which would make anatomic resection with pres- ervation of liver function impossible. Additional eligibility criteria included: (1) age ≤18 years and weight >30 kg; (2) no chemotherapy, radiotherapy or biologic therapy in the 4 weeks prior to the liver perfusion; (3) recovery from all side-effects of prior therapy; (4) an Eastern Cooperative Oncology Group (ECOG) performance status ≤2; and (5) adequate organ function as evidenced by serum biliru- bin <2.0 mg/dl, prothrombin time <2 s greater than the upper limit of normal, platelet count >100,000/μl, hemat- ocrit >27, white blood cell count >3,000/μl, and serum creatinine ≤1.5 mg/dl or creatinine clearance >60 ml/min. Patients with elevated hepatic transaminases secondary to the presence of metastatic disease in the liver were ineli- gible. Exclusion criteria were: (1) biopsy-proven cirrhosis; (2) portal hypertension; (3) pregnancy; and (4) uncorrect-
table coronary artery or pulmonary disease.

The study was approved by the US Food and Drug Administration (FDA), the University of Pittsburgh Insti-
tutional Review Board, and the University of Pittsburgh Cancer Institute (UPCI) Protocol Review Committee. The study was monitored by the UPCI independent data safety monitoring board and the principal investigators (H.Z. and D.L.B.). All patients read and signed an approved protocol-specific consent before enrolling in the protocol.

Study Design

Surgical Preparation and IHP Procedure

IHP was administered via a laparotomy incision. The liver was extensively mobilized in preparation for IHP to ensure that there was no leak of perfusate into the systemic circulation. The right and left lobes of the liver were released from their diaphragmatic attachments, and the retrohepatic inferior vena cava (IVC) was dissected out of the retroperitoneum from the level of the renal veins to the diaphragm, which included systematic identification and ligation of retroperitoneal venous tributaries and the right adrenal vein. This maneuver insured that there would be no leak of perfusate from the isolated segment of retrohepatic IVC. A prophylactic cholecystectomy and a periportal lymph node dissection were performed. The gastroduode-
nal artery (GDA) was dissected for 1–2 cm from the common hepatic artery. An external veno-veno bypass circuit was established by placing a cannula into the left femoral vein and advancing it into the infrarenal IVC and then advancing a second cannula through the internal jugular vein into the superior vena cava. This allowed maintenance of the systemic circulation by actively shunting IVC blood during treatment. Once the venous...
bypass had been established, the IHP circuit was constructed. The GDA was ligated distally. The inflow cannula for perfusion was positioned in the proximal GDA, and, once secured, a cross clamp was placed across the entire porta hepatitis, including the common hepatic artery, bile duct, and portal vein. The perfusion outflow cannula was inserted into the retrohepatic IVC via a percutaneous cannulation of the right femoral vein and a tourniquet was placed around the cannula at the level of the supraprenal infrahepatic IVC. The suprahepatic IVC was then cross-clamped, and once this had been accomplished, vascular isolation of the liver was considered complete, and perfusion was initiated. The perfusate consisted of approximately 500 ml Ringer’s lactate to which were added 2 units of packed red blood cells. Once perfusion was initiated, flow through the isolated circuit was maintained between 150 and 300 ml/min. Temperature probes were placed into the anatomic right and left lobes of the liver, and perfusate was heated to maintain hepatic hyperthermia of 40°C. Once hyperthermia was obtained and perfusion parameters were stable the specified dose of oxaliplatin was administered into arterial limb of the isolated perfusion circuit over 5 min. Oxaliplatin was prepared in the minimal volume possible for reconstitution of the specified dose. The liver was then perfused for 1 h during which samples for pharmacokinetics studies were drawn from the isolated circuit and systemic circulation at 5, 15, 30, 45, and 60 min. Following the 1 h perfusion, the isolated liver perfusion circuit was flushed with 3 l hextan solution to remove all drug-containing perfusate. The portal venous, hepatic arterial, and superior vein clamps were then removed and flow to the liver was reestablished. Following the 1 h experimental perfusion the HAI pump was then placed into the GDA stump.

Further Treatments

At the completion of the IHP treatment and a 6-week observation period, all patients received FUDR chemotherapy via the hepatic arterial pump, alternating with best systemic chemotherapy at the discretion of their treating physician.

Dose Escalation

The dosing schema for the trial is illustrated in Table 1. The starting dose of 5 mg/m², which is approximately 25-fold lower than the MTD of systemically administered oxaliplatin, was chosen because of concerns regarding potential unrecognized toxicity associated with delivering the oxaliplatin in the setting of a hyperthermic isolated perfusion circuit. The oxaliplatin dose was then doubled to 10 and 20 mg/m² for the next two cohorts, which consisted of one subject each. After reaching 20 mg/m², the oxaliplatin dose was escalated to 40 mg/m², and the study reverted to a standard 3 + 3 schema with sequential 50%, 33% or 25% dose escalations planned in successive cohorts (Table 1).

Study Endpoints

The primary endpoint of the study was to determine the MTD and DLT of oxaliplatin delivered via hyperthermic IHP. Because IHP was administered in the context of a major operative procedure, it was important to distinguish the contribution of the procedure itself from that related to dose escalation of oxaliplatin. As we have reported for previous IHP studies, toxicities were divided into systemic and regional (liver) categories. All toxicities were graded according to National Cancer Institute (NCI) Common Toxicity Criteria, version 2.0. Systemic DLT was defined as any grade III or IV major organ toxicity that was not reversible within 48 h. Because our previous experience with melphalan IHP demonstrated transient hepatic toxicity, regional hepatic DLT was scored as follows: (1) serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) > 10-fold the upper limit of normal at 2 weeks after IHP; (2) grade III or IV hyperbilirubinemia that did not resolve by 6 weeks after IHP; or (3) any hyperbilirubinemia in the first 6 weeks associated with clinical signs of veno-occlusive disease (VOD). Dose escalation was based on regional DLT.

Secondary endpoints included: (1) evaluating the response rate, duration of response, and survival of patients treated with hyperthermic oxaliplatin IHP followed by HAI/FUDR systemic combination therapy; and (2) determining the concentration of platinum in the IHP perfusate and plasma during the 60-min IHP and in biopsies of normal liver and tumor obtained at the end of the 60-min IHP. Responses were assessed by response evaluation

<table>
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<tr>
<th>TABLE 1 Oxaliplatin dose escalation scheme</th>
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a MTD
b DLT of grade V VOD and fulminant hepatic failure
criteria in solid tumors (RECIST) criteria at 6 weeks and 6 months following IHP. CEA levels were assessed at 2 weeks, 6 weeks, and 6 months after IHP.

Pharmacokinetics

Samples were obtained from the afferent and efferent limbs of the perfusion circuit before and at 5, 15, 30, 45, and 60 (end of IHP) min after addition of oxaliplatin to the perfusion circuit. Samples of peripheral venous blood were collected at the same times as perfusate as well as at 15, 30, 60, and 120 min after the end of the IHP procedure. All samples were collected in 5-ml heparinized vacutainers, immediately placed on ice, and then centrifuged at 1,000 × g for 10 min. The resulting perfusate and plasma supernatants were then stored at −70°C until analysis for platinum content. Ultrafiltrates of perfusate and plasma were prepared by placing a portion of each sample into an Amicon Centrifree micropartition device (Amicon Division, W. R. Grace, Beverly, MA, USA) and then centrifuging those devices at 2,000 × g for 20 min at 4°C. Wedge biopsies of normal liver and hepatic metastases were obtained prior to and at the conclusion of the IHP. Biopsies were rapidly weighed and then stored at −70°C until analysis for platinum content. Liver and tumor biopsies were homogenized in 3 parts (w/v) phosphate-buffered saline. Platinum concentrations in plasma, perfusate, their respective ultrafiltrates, and tissue homogenates were assessed with a Perkin–Elmer model 1100 flameless atomic absorption spectrometer (Perkin–Elmer, Norwalk, CT, USA) as previously described. Platinum concentrations were determined by comparison with a standard curve performed in an appropriate matrix on the same day as the assay. The area under the curve of platinum concentration versus time was calculated noncompartmentally using the log trapezoidal rule. The elimination constant (k_e) for ultrafilterable platinum in the afferent arm and volume of the overall IHP circuit (V_a) were estimated by fitting a one-compartment, open, linear model to afferent arm ultrafilterable platinum concentration versus time data. The half-life (t_{1/2}) of decline of ultrafilterable platinum in the afferent arm was calculated as 0.693/k_e. Clearance of ultrafilterable platinum from the afferent arm was calculated as (V_a)(k_e) and hepatic extraction of ultrafilterable platinum was calculated as (hepatic clearance)/(perfusion rate + hepatic clearance).

A control experiment was performed in which 68 mg (40 mg/m² × 1.7 m²) of oxaliplatin were added to the reservoir of a freestanding IHP circuit that was not connected to a patient. The hyperthermic perfusate was circulated for 60 min, and perfusate samples were obtained at the same times as in IHP studies involving patients. Per fusate samples were analyzed by flameless atomic absorption spectrometry, and pharmacokinetic parameters were estimated in the same manner as were perfusate samples obtained in patient studies.

Statistics

To determine whether maximal concentration (C_{max}) or area under curve (AUC) of ultrafilterable platinum in perfusate and the concentration of platinum in liver biopsies were proportional to oxaliplatin dose, we first normalized the variables to dose by computing the ratios of AUC/dose, C_{max}/dose, and liver platinum concentration/dose. The AUC used was the mean ultrafilterable platinum concentration in afferent and efferent arms but only afferent ultrafilterable platinum C_{max} was used. We then used the Jonckheere–Terpstra nonparametric procedure to test whether there was a trend for these ratios to increase (or decrease) with dose. A rejection of the null hypothesis of no increase (or decrease) would imply that perfusate ultrafilterable platinum C_{max}, AUC, or platinum concentration in liver biopsies did not increase linearly with dose. A similar procedure was used to determine whether the platinum concentration in liver was proportional to AUC, but in that case Spearman’s test was used. Spearman’s test was used to assess the association between maximum postperfusion serum bilirubin and ultrafilterable platinum C_{max}, AUC, and platinum concentration in liver biopsies. The Jonckheere–Terpstra nonparametric procedure was used to test the association between oxaliplatin dose and maximum postperfusion serum bilirubin. All p values are two-sided and considered significant when ≤0.05.

RESULTS

Patient Characteristics

Thirteen patients were enrolled in the protocol between November 2003 and September 2006 (Tables 1 and 2). All patients were deemed unresectable by independent review by two experienced liver surgeons. Three patients were deemed ineligible for isolated hepatic perfusion at the time of laparotomy. Two had extrahepatic metastases and one had severe hepatic steatosis. Ten patients underwent IHP with escalating doses of oxaliplatin (Table 1). The number of hepatic metastases ranged from 5–11 (median 6). Five of the ten patients who were treated had received prior systemic chemotherapy.

Adverse Events and Toxicities

Two patients experienced non-liver-related adverse events. The one patient treated with 5 mg/m² developed pleural effusion, and one of the six patients treated with
40 mg/m² developed early postoperative pneumonia and systemic inflammatory response syndrome (SIRS). All patients had evidence of transient liver injury as manifested by rises in AST and ALT. In all cases, AST and ALT returned to baseline by 2 weeks postprocedure. Seven patients demonstrated a rise in the serum bilirubin. There was no correlation between maximum serum bilirubin and oxaliplatin dose ($p = 0.91$), afferent ultrafilterable platinum $C_{\text{max}}$ ($p = 1.0$), AUC ($p = 0.81$) or concentration of platinum in the postperfusion liver biopsies ($p = 0.81$). In six patients, total bilirubin returned to baseline by 6 weeks postprocedure. The one patient treated with 60 mg/m² died after experiencing a progressive rise in bilirubin associated with development of overt liver failure and biopsy-proven VOD. There were no irreversible liver-related DLTs at dose levels <60 mg/m².

**Pharmacokinetics**

In the control perfusion circuit, concentrations of total platinum remained constant during the 60-min study. In contrast, concentrations of ultrafilterable platinum decreased monoeXponentially with a $k_e$ of 0.0085 min⁻¹, which corresponded to a $t_{1/2}$ of 81 min and, based on the estimated $V_d$ of 997 ml, a clearance of 8.5 ml/min.

Pharmacokinetic studies were successfully performed in nine patients. In each patient, concentrations of total and ultrafilterable platinum in perfusate decreased with time (Fig. 1). As expected, the percentage of total platinum accounted for by ultrafilterable platinum also decreased progressively with time, declining from 89 ± 6.1% and 87 ± 9.0% in the 5-min afferent and efferent samples, respectively, to 66 ± 7.6% and 66 ± 9.4% in the 60-min afferent and efferent samples, respectively (Fig. 1).

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<th>Characteristic</th>
<th>Patients enrolled = 13</th>
<th>Patients eligible = 10</th>
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<tr>
<td>Age (years)</td>
<td>50 (39–61)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Number of liver metastases</td>
<td>6 (5–11)</td>
<td></td>
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<tr>
<td>Preoperative CEA (ng/ml)</td>
<td>62 (4.3–589)</td>
<td></td>
</tr>
<tr>
<td>Number of prior chemotherapy cycles</td>
<td>5</td>
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<td>1–3</td>
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<td>&gt;3</td>
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Concentrations of ultrafilterable platinum in the afferent limb declined with a $t_{1/2}$ of 33 ± 20 min, and the estimated $V_d$ of the perfusion circuit was 1.18 ± 0.51 l. The estimated clearance of ultrafilterable platinum was 26 ± 5 ml/min, of which 8.5 ml/min was accounted for by 60 min of circulation in the circuit, and the remaining 16 ± 7 ml/min reflected hepatic clearance. There was little, if any difference, between platinum concentrations in afferent and efferent limbs of the perfusion circuit (Fig. 1), which was consistent with hepatic extraction of ultrafilterable platinum being estimated as 6 ± 3%. There were nonlinear dose-related increases in ultrafilterable platinum $C_{\text{max}}$ ($p = 0.083$) and exposure, as expressed by AUC ($p = 0.0099$), delivered by the perfusate (Fig. 2a and b). The ultrafilterable platinum $C_{\text{max}}$ and AUC associated with any IHP dose of oxaliplatin were much greater than those described in the literature for oxaliplatin administered intravenously.30–37 No ultrafilterable platinum was detected in the plasma of any patient during or after the hepatic perfusion. There were dose- and AUC-dependent increases in liver platinum concentrations (Fig. 3a and b). The relationship between liver platinum concentration and ultrafilterable platinum AUC ($p = 0.097$). Similar relationships were much less obvious for tumor (Fig. 3a and b). In all patients, the concentration of platinum in liver biopsies was greater than those in the corresponding paired tumor biopsy.

**Clinical Response and Survival**

Nine patients were evaluable for response because, as described above, one patient died of VOD and hepatic failure before response could be assessed. At 6 weeks,
seven of the nine evaluable patients demonstrated a >50% decrease from their preoperative CEA values in response to IHP alone; however, only two, one treated at 20 mg/m² and one treated at 40 mg/m², fulfilled RECIST criteria for partial response. Responses to the combined IHP and HAI therapy at 6 months (best response achieved) are summarized in Table 3. Among the nine patients who completed IHP and HAI treatments, there were five partial responses, one complete response, and two stable diseases (66% response rate). Two patients, each with unresectable bilobar metastases, were able to undergo subsequent resection. One patient had partial response (PR) that allowed for a subsequent trisegmentectomy. This patient survived 48 months before succumbing to liver and systemic recurrence. A second patient underwent resection of a single recurrence after an initial complete response in the liver. This patient remains with no evidence of disease (NED) at 48 months. Only one patient demonstrated progressive disease. Median time to progression in the liver was 15 months. Median overall survival was 25 months.

**DISCUSSION**

IHP in combination with HAI therapy is a proven regional delivery system for treatment of patients with unresectable liver metastases from colorectal cancer. Several studies have confirmed the ability of IHP to produce meaningful response rates in the liver, even in patients who have failed newer systemic chemotherapy regimens. Nearly all studies utilizing IHP in patients with colorectal metastases have used melphalan as the chemotherapeutic agent in the isolated circuit. As the next
Isolated Hepatic Perfusion with Oxaliplatin

phase in the development of this regional therapy, we studied the use of oxaliplatin IHP. There were substantial preclinical and clinical data to support this clinical study. In vitro, oxaliplatin acts after a brief exposure and its activity is concentration dependent. Oxaliplatin has substantial activity against advanced colorectal cancer and has been delivered as an HAI with no significant hepatic DLT.38–43 In addition, cultured colorectal tumor cell lines demonstrated transient cholestasis. In this trial, there was hepatic toxicity through the first three dose cohorts, which was consistent with our previous experience with melphalan IHP. As in our previous experience, the majority of patients demonstrated transient cholestasis. In this trial, there was no obvious relationship between maximum serum bilirubin after IHP and dose of oxaliplatin delivered or any of the pharmacokinetic parameters examined (C_max or AUC for platinum). The first and only hepatic DLT observed in the current study occurred at 60 mg/m². This DLT was biopsy-proven VOD, which resulted in progressive, fulminant hepatic failure, and death of the patient. This subject received the highest C_max and AUC of oxaliplatin delivered by IHP. This patient had also received > 10 cycles of systemic oxaliplatin prior to IHP, the most of any patient enrolled in the trial. Nevertheless, because VOD was the first DLT observed at the MTD in previous phase I trials of melphalan IHP and because of concerns about nonlinearity in the AUC of oxaliplatin delivered by IHP, the data safety monitoring board and investigators decided to stop oxaliplatin dose escalation.15 An additional three patients were treated at the 40 mg/m² dose level without any hepatic DLT.

The appropriate method for dosing IHP circuits is controversial.46,47 We chose to calculate oxaliplatin dose based on body surface area (BSA) because BSA has been demonstrated to represent liver volume adequately.48,49 The pharmacokinetic data from the current study provide important information for considering the appropriate dosing of oxaliplatin by IHP. The V_d of oxaliplatin calculated for each patient agreed well with the actual volume of the IHP circuit. Not unexpectedly, the circuit volumes were much less than the V_d reported for oxaliplatin delivered as a 2-h intravenous infusion.30–32,34–36 Correspondingly, the C_max of ultrafilterable platinum delivered to the liver via IHP were much greater than the peak plasma concentrations of ultrafilterable platinum C_max produced by a standard 2-h intravenous infusion of the oxaliplatinum MTD of 130 mg/m².30–32 Moreover, the C_max delivered by IHP occurs immediately after addition of oxaliplatin to the IHP circuit, whereas ultrafilterable platinum concentrations rise much more slowly during the 2-h systemic infusions of oxaliplatin. As with C_max, the oxaliplatin AUC delivered by IHP was much greater than that expected from a similar dose delivered systemically.50,51 In fact, the AUC associated with 40 mg/m² of oxaliplatin delivered by IHP was similar to those reported for 130 mg/m² systemic doses. This observation is consistent with the fact that renal clearance accounts for 30–50% of the clearance of systemically delivered oxaliplatin and the inability of the kidneys to participate in the clearance of oxaliplatin delivered by IHP. Each of these observations may be mechanistically related to the hepatotoxicity and dose-limiting VOD observed in the study. The pharmacokinetic data also indicated no systemic exposure to oxaliplatin, very low extraction by the liver of ultrafilterable platinum from the IHP perfusate, and no increased delivery of platinum to the tumor as compared with normal liver. These observations have important implications regarding oxaliplatin delivered via an isolated circuit. First, it confirms the ability of the isolated hepatic perfusion to achieve near-zero systemic platinum exposure. Second, it suggests no benefit in terms of dose intensification, as the regional toxicity of oxaliplatin delivered into a hyperthermic circuit was hepatic and observed at platinum exposures equivalent to doses achieved at the systemically delivered MTD. It is interesting to note that the DLT for systemically delivered oxaliplatin is not hepatic toxicity.

We observed no correlation between the dose of administered platinum and tumor platinum. However, these

### TABLE 3 Clinical responses to combined IHP and HAI therapy

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Dose (mg/m²)</th>
<th>Radiographic response at 6 months (RECIST)</th>
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<tr>
<td>1</td>
<td>5</td>
<td>SD&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>2</td>
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<tr>
<td></td>
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<td>Response rate 66%</td>
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<sup>a</sup> Stable disease  
<sup>b</sup> Partial response  
<sup>c</sup> Complete response  
<sup>d</sup> Progressive disease
results should be taken with some caution as the tumors biopsied following IHP represented surface biopsies of the most superficial tumors. Subsequent studies will utilize core biopsy material from the center of the tumors in an attempt to quantitate tumor platinum uptake better.

Although the primary endpoint of this trial was toxicity, we did observe evidence of clinical efficacy. Because many of the early radiographic changes following IHP are cystic/necrotic changes that are not easily tracked by RECIST criteria, and because a decrease in CEA has been reported to correlate with clinical responses in other trials, we chose to follow serum CEA concentrations as a biomarker of the efficacy of the IHP alone.52 Eight of the nine evaluable patients demonstrated decreases in their serum CEA levels during the first 6 weeks following IHP. These data suggest that the one-time IHP was associated with significant antitumor activity. The overall regional treatment algorithm (IHP followed by HAI and systemic chemotherapy) was associated with an overall 66% response rate. This is slightly lower than the response rate in our previously reported phase II trial that used melphalan-based IHP in patients with hepatic metastases from colon cancer, but it is encouraging given that the current study was a phase I trial.15 Median overall survival was 25 months, which is comparable to, if not better than, that associated with the best systemic regimens used to treat patients with similar tumor burdens.53,54 This suggests that, despite not achieving increased local concentrations of oxaliplatin, a single delivery through the hyperthermic isolated circuit is associated with significant antitumor activity, and supports the concept that aggressive regional control of hepatic metastases may improve overall survival when combined with best systemic chemotherapy. It also demonstrates that an aggressive regional treatment approach combined with systemic chemotherapy did not have a negative impact on survival.

In conclusion, hyperthermic IHP with oxaliplatin was safe and feasible at a dose of 40 mg/m². The ability to obtain complete vascular isolation with open IHP was confirmed. No selective pharmacokinetic advantage in dose intensification was observed for oxaliplatin delivered through the isolated circuit. The response rate in this small phase I study was encouraging. Based on these results, a phase I/II study examining IHP with a combination of oxaliplatin (40 mg/m²) and increasing doses of 5-FU in conjunction with best systemic chemotherapy is currently being performed. It is important to note that this aggressive locoregional approach is not thought to be a substitute for systemic chemotherapy, but rather we believe should be applied in conjunction with effective systemic chemotherapy. The ultimate goal for this approach is to design a locoregional/systemic treatment regimen that results in near 100% in-liver response rates for those patients not able to be rendered disease free from surgical resection. We believe that this approach similar to combining surgery with systemic chemotherapy may improve overall survival.

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REFERENCES


