Percutaneous Isolated Hepatic Perfusion for Chemotherapy

A Phase 1 Study

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Background: Increasing the drug concentration in tumors may produce massive tumoral response. By using a variety of hepatic vascular isolation techniques, high concentrations of chemotherapeutic drugs may be achieved in the hepatic vascular bed.

Hypothesis: Complete percutaneous isolated hepatic perfusion (IHP) is feasible and safe.

Design: Case series.

Setting: The hepatobiliary unit of a university hospital.

Patients: Ten patients with irresectable and chemoresistant hepatic tumors were eligible for study participation; 4 patients with hepatic metastases of breast cancer, gastric cancer, colorectal cancer, and cholangiocarcinoma were included.

Intervention: Patients received 3 successive courses of chemotherapy by IHP. The first course was given at laparotomy, and the next 2 courses were given percutaneously. The interval between courses was 3 to 6 weeks. Each course involved IHP of the liver for 15 to 30 minutes, without oxygenation, with 1 to 3 boluses of melphalan (15 mg).

Main Outcome Measures: Morbidity and mortality.

Results: Ten IHPs were performed (4 at laparotomy and 6 percutaneously). Concentrations of melphalan in the extracorporeal circulation were 10 times higher than those in the systemic circulation. Percutaneous IHPs had more leakage than those at laparotomy. However, hepatotoxicity was minimized. One patient experienced hepatic artery thrombosis, and 3 had severe neutropenia. Minor complications included ascites and pleural effusion. No deaths were observed 2 months after the last IHP. One partial response was observed (hepatic metastases of breast cancer).

Conclusion: Percutaneous IHP for intensive chemotherapy is less aggressive and less hepatotoxic than IHP at laparotomy and may be iterative.

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Although the best therapeutic option for hepatic tumors is surgical resection, approximately 85% to 90% of these tumors are inoperable. Adjuvant treatments may be used to increase the proportion of resectable tumors, resulting in an associated improvement in survival. As demonstrated in the case of hepatic colorectal metastases, down-staging systemic chemotherapy, portal vein embolization, local destruction, and 2-stage hepatectomy increase the proportion of resectable nodules and improve median survival time. However, despite such adjuvant treatment, approximately 60% of metastases remain inoperable owing to chemoresistance or the number or location of metastatic nodules. Therefore, other cytotoxic agents and protocols based on systemic administration diffusion are under evaluation. In addition, experimental data and several clinical trials have demonstrated improved tumoral response with higher drug concentrations. These studies include intensive systemic chemotherapy followed by bone marrow transplantation, hepatic intra-arterial chemotherapy alone or under hepatic venous isolation, and isolated limb and pelvic perfusion.

We investigate herein the delivery of local chemotherapy under total vascular exclusion based on a technique first described in 1960. In the ensuing 40 years, in contrast to advances in isolated limb perfusion, few series of chemotherapy under total vascular exclusion have been described. High morbidity and mortality rates have been reported, and, in the absence of proof of a beneficial effect, such
treatment has not been adopted. More recently, interventional radiology has prompted the development of specialized double-balloon catheters that allow a minimally invasive approach to isolation of the vena cava. Therefore, to increase doses with minimal procedure-related complications, we developed a protocol for isolated hepatic perfusion (IHP) characterized by repeated courses and the use of minimally invasive techniques. Given our experience in radiologic interventional techniques, and following a preclinical experimental study, we moved to a clinical phase 1 study, which is reported herein.

METHODS

PROTOCOL DESCRIPTION

Between September 1, 1998, and April 30, 2001, patients with primary or secondary liver malignancies showing no response to conventional treatment received information regarding chemotherapy under vascular exclusion. Inclusion criteria were as follows: not being enrolled in another anticancer research protocol, the absence of chemotherapy or radiotherapy 4 weeks before inclusion, the absence of bone marrow insufficiency (documented, if necessary, by an iliac biopsy), a creatinine level less than 1.7 mg/dL (<150 µmol/L), a white blood cell count greater than 3.0 × 10^9/L, a polymorphonuclear cell count greater than 1000/µL, a hemoglobin level greater than 10.0 g/dL, a platelet count greater than 80 × 10^9/L, an albumin level greater than 2.0 g/dL, a calcium level less than 12.0 mg/dL (<3.00 mmol/L), a total bilirubin level less than 2.0 mg/dL (<34 µmol/L), aspartate and alanine aminotransferase levels less than 5 times the reference values, and compliance for clinical and radiologic follow-up. Exclusion criteria were contraindication to hepatic vascular exclusion (heart disease or respiratory insufficiency), occurrence of a severe adverse effect (deep venous thrombosis, pulmonary embolism, arterial thrombosis, or acute pancreatitis), and patient withdrawal. Patients fulfilling the inclusion criteria received oral and written information about the study and gave written informed consent. Hepatic arterial anatomy was documented by preoperative angiography in the following cases: suspicion of anatomic variants or a history of previous hepatectomy. A laparotomy was performed to confirm the absence of nonresectable extrahepatic tumor and to assess technical feasibility. Abdominal malignant lymph nodes were not considered as an exclusion criteria if they were resectable. The first course of chemotherapy was performed at the same operation, defining the beginning of the protocol (day 0). Second and third courses were performed 3 to 6 weeks later using minimally invasive techniques. The end of the protocol was defined by the date of the computed tomographic (CT) scan performed 1 month after administration of the last course.

TECHNICAL DESCRIPTION

First Course of Chemotherapy at Laparotomy

An 8F polyurethane catheter (Clinical Plastic Products SA, La Chaux-de-Fonds, Switzerland) (Figure 1) was inserted into the lumen of the gastroduodenal artery, and the tissues supplied were checked by methylene blue injection. Hepatic ligaments were divided, and the right adrenal vein was ligated. A cannula was inserted into the retrohepatic vena cava and was then connected to an extracorporeal perfusion system using a nonocclusive roller pump (Sofracob SA, Reventin Vaugris, France). The liver was irrigated in a recirculating fashion via the gastroduodenal catheter. The perfusate consisted of 300 mL of Ringer lactate solution plus blood cells contained in the vascular bed of the liver. After total vascular exclusion, perfusion flow was increased to 200 to 300 mL/min, and a bolus (15 mg) of melphalan (Alkeran; GlaxoSmithKline, Marly-le-Roi, France) was injected into the circulating perfusate via the gastroduodenal arterial line. The leak rate was appreciated by measurements of systemic melphalan levels. Results were available within 2 to 4 days of IHP, enabling the anticipation of marrow aplasia and thus initiation of granulocyte colony-stimulating factor treatment. After 15 to 30 minutes, the effluent line was opened, hepatic outflow was discarded, and perfusate was replaced by 1 L of 0.9% isotonic sodium chloride solution for 5 minutes to remove residual melphalan from the hepatic vascular space before reperfusion. Vascular exclusion of the liver did not exceed 45 minutes. Before closure of the abdomen, the gastroduodenal catheter was connected to a subcutaneous chamber, and the luer lock connection was placed under the skin (Figure 1). The chamber was injected with heparin sodium on a weekly basis to prevent thrombosis. A silicone-lined nylon thread was positioned around the common hepatic artery and exteriorized in the left upper quadrant to allow arterial occlusion during further percutaneous procedures. A silicone drain was placed under the liver.

Second and Third Courses of Chemotherapy Using the Percutaneous Technique

The procedure was performed under general anesthesia using ultrasound (3.5-MHz probe) and fluoroscopic guidance. The luer lock connection of the gastroduodenal catheter was divided and opened, and hepatic arteriography was performed before and after occlusion of the common hepatic artery by traction on the nylon thread. This maneuver checked the arterial selectivity of the infused territory (Figure 2). A distal portal branch was cannulated under ultrasound guidance using a 22-gauge needle and then catheterized; an 8F occlusive catheter (Boston Scientific Corp, Natick, Mass) was positioned in the portal vein according to the Seldinger technique. Through a small groin incision, the long saphenous vein was divided, and a rigid vascular leader was introduced into the vena cava. After progressive dilation, an 18F double-balloon catheter (Clinical Plastic Products SA) was inserted into the retrohepatic vena cava, and a bolus of heparin (100 IU/kg) was injected into the general circulation. Vascular exclusion (Figure 3) was achieved according to the following steps: (1) occlusion of the hepatic...
artery by traction of the thread, (2) inflation of the portal vein occlusive balloon, (3) inflation of the inferior vena cava balloon, (4) inflation of the superior vena cava balloon, (5) traction on the double-balloon catheter to maintain perfect occlusion between the superior balloon and the lower part of the right atrium, (6) retrograde injection of contrast fluid into the internal lumen of the double-balloon catheter to check for the absence of leakage, and (7) a check of the position of each balloon every 3 minutes. Extracorporeal circulation was then achieved between the double-balloon catheter and the gastroduodenal catheter. One to 3 boluses (15 mg) of melphalan were injected at intervals of 5 minutes and circulated for 15 to 30 minutes, followed by 5 minutes of isotonic sodium chloride solution irrigation, after which the liver was reperfused. The leakage rate of melphalan was appreciated by measurements of systemic levels, with results available within 2 to 4 days of IHP. Two milliliters of biological glue (Tissucol; Baxter SA–Division Bioscience, Maurepas, France) was injected into the transparenchymal tract of the portal vein occlusive catheter. The gastroduodenal catheter was reconnected to the chamber and replaced under the skin. Low-molecular-weight heparin was systematically used after surgery to prevent deep-vein thrombosis.10,11

MELPHALAN AND BIOLOGICAL ASSAYS

Perfusate and systemic plasma samples were obtained 3, 5, 10, 15, 30, and 120 minutes after administration of the first bolus of melphalan. Samples were collected in lithium-heparinized glass tubes, immediately placed on ice (in darkness), and centrifuged within 4 hours. Serum was stored at −80°C until assayed by high-performance liquid chromatography (Bakerbond C18 column; J.T. Baker, Phillipsburg, NJ), with detection at 260 nm. Blood cells counts, enzyme concentrations, and coagulation factors were assayed using standard automated techniques.

STATISTICAL ANALYSIS

Data are presented as mean±SD. Comparative statistics between surgical and percutaneous data were performed using t tests (unpaired); P<.05 was considered significant.

RESULTS

STUDY POPULATION

Of 10 patients who consented to the protocol, 3 underwent intent-to-treat surgery but were excluded for tumoral infiltration of the hepatic ligament (n=2) or massive subcapsular hematoma of the liver before vascular exclusion (n=1). Three patients were excluded before laparotomy for tumor progression (n=2) or sepsis (n=1). Finally, 4 patients received 10 courses of chemotherapy, representing the study population (see the “Summarized Case Reports” subsection).

PHARMACOKINETICS

Levels of melphalan in the perfusate were similar during IHP performed at laparotomy and percutaneously. After administration of the bolus, a peak concentration was observed that decreased sharply within 5 minutes to a plateau of values that decreased slowly from 4000 to 3000 ng/mL. If a second bolus was injected, the values were approximately 5500 ng/mL (Figure 4). Sys-

![Figure 2](https://archsurg.jamanetwork.com/)

**Figure 2.** Intraoperative angiograms obtained via the gastroduodenal catheter (arrow) before (A) and after (B) nylon thread traction demonstrating the absence of reflux.

![Figure 3](https://archsurg.jamanetwork.com/)

**Figure 3.** The process of percutaneous vascular exclusion. 1 Indicates perfusate with chemotherapy; 2, double-balloon catheter introduced through a groin incision; 3, gastroduodenal catheter; 4, hepatic artery clamped by a silicone-lined nylon thread; and 5, portal vein percutaneously clamped by a balloon catheter.

![Figure 4](https://archsurg.jamanetwork.com/)

**Figure 4.** Plasmatic concentrations of melphalan during isolated hepatic perfusion in liver perfusate (diamonds) and in systemic circulation (circles).
**Table 1. Morbidity After Chemotherapy by Isolated Hepatic Perfusion Performed at Laparotomy vs Percutaneously**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Laparotomy (n = 4)</th>
<th>Percutaneous (n = 6)</th>
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</thead>
<tbody>
<tr>
<td>Melphalan dose, mg</td>
<td>15</td>
<td>15-45</td>
</tr>
<tr>
<td>Hospital stay, mean ± SD, d</td>
<td>14 ± 3</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>Blood transfused during surgery, mean ± SD, l/day</td>
<td>5 ± 2</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Hepatic artery thrombosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ascites</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Parietal hernia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Major asthenia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia (neutrophil count &lt;10000/μL)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia (neutrophil count &lt;5000/μL)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt;50 x 10^3/μL)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are given as number of patients, except where indicated otherwise.

**Table 2. Hepatic and Renal Toxicity After Chemotherapy by Isolated Hepatic Perfusion Performed at Laparotomy vs Percutaneously**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Laparotomy</th>
<th>Percutaneous</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time, s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>15.8 ± 0.4</td>
<td>16.8 ± 3.0</td>
<td>.55</td>
</tr>
<tr>
<td>Day 1</td>
<td>27.8 ± 3.3</td>
<td>24.4 ± 2.7</td>
<td>.13</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>50 ± 17</td>
<td>29 ± 4</td>
<td>.02</td>
</tr>
<tr>
<td>Day 1</td>
<td>151 ± 57</td>
<td>38 ± 14</td>
<td>.001</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>0.9 ± 0.2</td>
<td>0.8 ± 0.1</td>
<td>.33</td>
</tr>
<tr>
<td>Day 1</td>
<td>1.0 ± 0.2</td>
<td>0.7 ± 0.1</td>
<td>.02</td>
</tr>
</tbody>
</table>

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

Data are given as mean ± SD.

**MORBIDITY AND MORTALITY**

There were no deaths within 2 months after the last course. Minor adverse effects included ascites via the abdominal drain and pleural effusion (Table 1). Major complications were hepatic artery thrombosis (patient 3) and veno-occlusive disease (VOD) (patient 1). No hepatic insufficiency or multiple organ failure was observed. After percutaneous IHP, postoperative increases in aminotransferase and creatinine levels were significantly less than those observed with the open technique (Table 2).

However, grades 3 and 4 neutropenia were observed only after percutaneous IHP (once after the second course and 3 times after the third course). Granulocyte colony-stimulating factor administration was needed in 1 case only. One grade 3 thrombocytopenia was observed after the third course that did not require platelet transfusion.

**SUMMARIZED CASE REPORTS**

**Patient 1**

A 54-year-old woman with hepatic metastases from a breast adenocarcinoma (T2 N0 M0) was treated initially by local excision and radiotherapy. On discovery of metastases 3 years later, she was treated for 6 years with 4 lines of systemic chemotherapy and underwent 2 hepatectomies (left-sided hepatectomy and then wedge resections in segments 4 and 7). Her disease recurred with a carcinoembryonic antigen (CEA) of 94 ng/mL (N < 5), a cancer antigen 15/3 (CA15/3) of 1500 U/L (N < 35), and a CT scan showing massive hepatic involvement by multiple hypodense nodules (day –31) (Figure 5A), with progression compared with CT images from 3 months earlier. In the absence of an alternative, chemotherapy by IHP was suggested. Because of difficulty in mobilizing the remnant right side of the liver owing to dense adhesions, the suprahepatic vena cava was clamped using a transpericardial approach. During the second course of chemotherapy (day 41), incomplete occlusion by the superior vena cava balloon caused major leakage of the first 15-mg bolus of melphalan. After correction of the vascular occlusion, a second bolus of melphalan was successfully perfused in the liver for 15 minutes. During the third course (day 83), 2 boluses of melphalan circulated for 15 minutes uneventfully. Postoperative ascites appeared after the first course of chemotherapy and recurred for 6 months, requiring weekly paracentesis. A hepatic biopsy sample obtained 1 month after the end of the protocol (day 112) showed obstruction of small hepatic veins, suggesting a VOD and persistence of tumor cells. A CT scan (day 105) revealed a 50% response (Figure 5B), and CA15/3 and CEA levels were reduced. A CT scan (day 105) revealed a 50% response (Figure 5B), and CA15/3 and CEA levels were reduced.

**Figure 5.** Liver metastases of breast cancer were treated with 3 successive courses of melphalan by isolated hepatic perfusion. Computed tomographic scans are compared 1 month before (A) and 1 month after (B) 3 such courses.

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tine antibody trastuzumab (Herceptin; Roche, Neuilly-sur-Seine, France) was then administrated in association with vinorelbine tartrate (Navelbine; Pierre Fabre Oncologie, Boulogne, France), leading to normalization of the CEA and CA15/3 levels 10 months later. Con-

talateral breast cancer occurred 1 year later. This pa-

rient was alive with hepatic metastases 31 months after the end of the IHP protocol.

**Patient 2**

A 64-year-old man with synchronous hepatic metastases from colorectal cancer was treated as follows: (1) rectal anterior resection plus multiple limited hepatic re-

sections and first-line chemotherapy with fluorouracil (Fluorouracile; Dako
ta Pharm, Creteil, France) and folic

nic acid (Calcium Folinate; Dako
ta Pharm); (2) second-

line chemotherapy with fluorouracil, folic acid, and oxaliplatin (Eloxatin; Sanofi Synthelabo, Paris, France); (3) third-line chemotherapy with fluorouracil, folic acid, and irinotecan hydrochloride (Campto; Aventis, Paris, France) (partial response); (4) left-sided hepatec-
tomy and partial resections in the right side of the liver (complete response); (5) chemotherapy with fluorou-

racil, folic acid, and irinotecan for 2 months; (6) a third hepatectomy for 2 metastases removed by wedge resection; (7) chemotherapy with fluorouracil, folic acid, and oxaliplatin for 6 months; (8) percutaneous radiofrequency of 2 metastases (partial response); and (9) chemotherapy with fluorouracil, folic acid, and irinotecan. At this stage, 9 progressive hepatic nodules were noted on CT images, with maximal diameters of 10.5 cm. In the absence of an alternative treatment, chemotherapy by IHP was proposed. No perito-

nal carcinomatosis was noted during laparotomy, but 1 metastatic lymph node at the mesenteric root was resected. Mobilization of the remnant right side of the liver was not possible, and the suprahepatic vena cava was clamped via a transpericardial approach. One 15-mg bolus of melphalan circulated for 15 minutes. Ascites was the main postoperative adverse effect. The level of CEA decreased from 360 to 119 ng/mL. Second and third courses (days 39 and 63, respectively) were well tolerated despite leakage due to a nonocclusive position of the superior bulo

on during the third course. Melphalan doses of 15 mg and 15 mg × 2 were administrated during the second and third courses, respectively. Chemoperfusions did not exceed 15 minutes. One month after the third course, the CEA level reached 621 ng/mL, and a CT scan confirmed disease progression. No other treatment was proposed, and the patient died 1.6 months later (day 146) of terminal disease.

**Patient 3**

A 63-year-old man had a 9 × 10 × 6-cm sclerotic cholan-

gio carcinoma compressing the hilum of the liver. After left-sided transhepatic biliary drainage, he received 5 courses of chemotherapy with gemcitabine hydrochloride (Gemzar; Eli Lilly and Co, Saint-Cloud, France) and cisplatin (Cisplaty; Aventis) without effect. Chemotherapy by IHP was proposed. No extrahepatic disease was observed during laparotomy. He received 1 bolus of 15 mg for 15 minutes. After the first course, ascites occurred and γ-glutamyl transpeptidase decreased from 9 to 3 times the reference value. Further courses could not be given because of hepatic artery thrombosis, and no other treatment was proposed. Because stable disease was noted on CT images (9 × 11 × 7 cm at day 63 and 8 × 11 × 7 cm at day 350), transplantation with a domino liver was attempted 15 months later. However, hyper-

vascularization around the liver prevented the procedure from being performed. The patient remained without treatment and died 28 months later of progressive disease.

**Patient 4**

A 61-year-old woman with synchronous hepatic metastases from a resected gastric cancer underwent chemotherapy with epirubicin hydrochloride (Farmorubicin; Pharmacia SAS, Guyancourt, France), fluorouracil, folic acid, and carboplatin (Paraplatin; Bristol-Myers Squibb, Puteaux, France) for 6 courses and then with docetaxel (Taxotere; Aventis) and fluorouracil. Chemotherapy by IHP was suggested in the face of progressive disease. At laparotomy, 13 hepatic and celiac lymph nodes were resected, 5 of which were metastatic but with no other macroscopic extrhepatic extension. One 15-mg bolus of melphalan was perfused for 30 minutes. After a decrease in the CEA level from 2293 to 1403 ng/mL, progression of the disease could not be stopped by the second (day 21) and third (day 46) courses despite dose escalation (15 mg × 2 for 30 minutes and 15 mg × 3 for 30 minutes during the second and third courses, respectively). Biliary compression was treated 2 months later by a percutaneous prosthesis. The patient died 4 months after the end of the protocol (day 198) of terminal disease.

**COMMENT**

We performed 10 courses of chemotherapy by IHP, com-

bining classic and percutaneous techniques, and demon-

strated that perfusions could be iterative without morta-

lity. To our knowledge, this is the first study of percutaneous hepatic vascular exclusion including portal, arterial, and venous clamping.

**LIVER PERFUSION AND TOXIC EFFECTS**

Performing surgical IHP requires experience in liver sur-

gery and extracorporeal bypass. After this procedure, 2-month mortality of 9% is reported in the literature (30 of 319 published cases) (Table 3), with Alexander et al.20 citing mortality of 6% in their experience of 100 cases. Postoperative hepatic insufficiency was the main cause of mortality (Table 3). For this reason, we adopted a sim-

plified method of liver perfusion characterized by a short period of warm ischemia, single-route perfusion (arterial only), and a simple perfusate medium.23 Under these
conditions, no cases of postoperative liver insufficiency were observed. The main hepatic toxic effect observed was VOD (patient 1). A similar phenomenon (ie, VOD) may explain the postoperative ascites and pleural effusion that were frequently observed after each IHP (Table 1). Several other studies report VOD after IHP with melphalan. The risk of developing VOD is increased by the cumulative toxic effects of different chemotherapeutic drugs, and because most patients eligible for IHP had received several lines of chemotherapy, they were potential candidates for developing VOD. Therefore, to achieve accurate delivery of melphalan and to avoid excessive hepatic toxic effects, we calculated doses according to the estimated liver weight, without reference to body weight. This gave a dose range of 10 to 30 mg/kg of liver parenchyma, which we assumed to be less toxic than doses used in other studies (0.5-4.0 mg/kg of body weight).

### PERCUTANEOUS IHP

We used established methods for percutaneous vena cava occlusion and portal vein access. However, we customized an arterial infusion device to accept a high-flow regimen and to allow minimally invasive access (Figure 1). The clamping method of the common hepatic artery (Figures 2 and 3) is well-known in our department since it has been used for several years as adjuvant treatment for neuroendocrine metastases. Although uncomfortable, this simple system allows easy clamping of the common hepatic artery and avoids complications associated with endovascular arterial maneuvers. Taken together, these techniques allowed a simple percutaneous hepatic vascular exclusion. Pharmacologic results demonstrate that concentrations of the drug administrated into the liver were similar to those achieved after IHP at laparotomy (Figure 4). However, leakage occurred during percutaneous IHP and induced systemic toxic effects, that is, neutropenia and thrombocytopenia. Several technical points may explain the leakage. First, the shortness of the human suprahepatic vena cava, in contrast to that of the pig, made its occlusion with a balloon difficult. Second, the veins around the common bile duct were not occluded by the portal occlusive balloon. Third, some diaphragmatic veins could be occluded during the surgical procedure by a surgical clamp but not during the percutaneous phase by a balloon. Furthermore, spontaneous deflation of balloons has been reported. Therefore, to avoid major hematomic toxic effects in the case of massive leakage, we used 15-mg boluses

**Table 3. Mortality and Morbidity After Isolated Hepatic Perfusion Reported in the Literature**

<table>
<thead>
<tr>
<th>Source</th>
<th>Perfusions, No.</th>
<th>2-mo Deaths, No.</th>
<th>Main Perioperative Complications</th>
<th>Cytotoxic Agents</th>
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<tr>
<td>Skibba and Quebbeman,19 1986</td>
<td>8</td>
<td>2</td>
<td>Lethal hepatotoxicity (n = 2)</td>
<td>T°</td>
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<tr>
<td>Schwemmle et al,19 1987</td>
<td>50</td>
<td>4</td>
<td>Pleural effusion (n = 9)</td>
<td>5FU, MMC, CDDP, T°</td>
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<td></td>
<td></td>
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<td>Hemorrhage (n = 3)</td>
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<td></td>
<td></td>
<td></td>
<td>Sepsis (n = 2)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Cardiac disturbances (n = 3)</td>
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<td></td>
<td></td>
<td></td>
<td>Subphrenic abscess (n = 1)</td>
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<td>Aigner,20 1988</td>
<td>55</td>
<td>3</td>
<td>Not reported</td>
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<tr>
<td>Hafström et al,21 1994</td>
<td>30*</td>
<td>8</td>
<td>MOF (n = 4)</td>
<td>L-PAM, CDDP, T°</td>
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<td>Marinelli et al,22 1996</td>
<td>9</td>
<td>1</td>
<td>VOD (n = 4)</td>
<td>MMC</td>
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<td>Reoperation (n = 2)</td>
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<td>Alexander et al,23 1998</td>
<td>34</td>
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<td>VOD (n = 1)</td>
<td>L-PAM, TNF, T°</td>
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<td>Oldhafer et al,24 1998</td>
<td>12</td>
<td>2</td>
<td>MOF (n = 2)</td>
<td>MMC, L-PAM, TNF, T°</td>
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<td>Myocardial infarction (n = 1)</td>
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<td>Lethal hepatotoxicity (n = 1)</td>
<td></td>
</tr>
<tr>
<td>de Vries et al,25 1998</td>
<td>50</td>
<td>3</td>
<td>ARDS (n = 1)</td>
<td>L-PAM, TNF, T°</td>
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<td>Lethal coagulopathy (n = 1)</td>
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<td>Hepatic artery thrombosis (n = 1)</td>
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<tr>
<td>Lindner et al,26 1999</td>
<td>11</td>
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<td>ARDS (n = 1)</td>
<td>INF, L-PAM, TNF, T°</td>
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<td>Reoperation (n = 8)</td>
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<td>MOF (n = 1)</td>
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<td>Hepatorenal syndrome (n = 1)</td>
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<td></td>
<td>ARDS (n = 1)</td>
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<tr>
<td>Alexander et al,27 2000</td>
<td>22</td>
<td>1</td>
<td>MOF (n = 1)</td>
<td>L-PAM, TNF, T°</td>
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<tr>
<td>Bartlett et al,28 2001</td>
<td>51†</td>
<td>1</td>
<td>VOD (n = 1)</td>
<td>L-PAM, TNF, T°</td>
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<tr>
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<td>Hepatic artery thrombosis (n = 1)</td>
<td>L-PAM</td>
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<td>VOD (n = 1)</td>
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**Abbreviations:** ARDS, adult respiratory distress syndrome; CDDP, cisplatin; 5FU, fluorouracil; INF, interferon; L-PAM, melphalan; MMC, mitomycin C; MOF, multiple organ failure; T°, hyperthermia (39°C-41°C); TNF, tumor necrosis factor; VOD, veno-occlusive disease.

*One patient had 2 isolated hepatic perfusions.

†Twenty-six cases of colorectal metastases, including the death, were probably included in the study by Alexander et al.33
of melphalan that were repeated only if perfect vascular occlusion was obtained.

MELPHALAN AND OTHER DRUGS

Melphalan is the main drug used in experimental and clinical studies of IHP.42,21,23,24,26 Its pharmacokinetic properties make it the drug of choice for IHP because of its short half-life, rapid uptake by the liver, and immediate effect as an alkylating agent.30,32,38 We did not use tumor necrosis factor because leakage of more than 1% is associated with substantial hemodynamic disturbance.30 Other drugs were excluded for the following reasons: mitomycin C because of its association with VOD,22,24 cisplatin because of its low liver uptake,40 and fluorouracil because of its poor pharmacokinetic benefits in IHP.43 Using melphalan alone, we observed a clear antitumoral effect in the case of breast cancer metastases (Figure 5). In this case, tumoral progression was exponential and was stopped by iterative IHP. This result is consistent with the beneficial effect of melphalan in this type of cancer.34 However, for our 3 other cases, resistance to melphalan occurred after the first course.

CONCLUSIONS AND PERSPECTIVES

These data demonstrate that percutaneous IHP is feasible and associated with fewer postoperative hepatic toxic effects compared with the surgical procedure (Table 2).30 However, we acknowledge that percutaneous IHP does not provide the same degree of isolation as the operative approach. Therefore, a pharmacologic adjustment was necessary considering the frailty of the patients in question. Technical improvements in the minimally invasive approach for IHP are possible with new endovascular equipment and laparoscopic techniques. In terms of antitumor efficiency, intensive chemotherapy by IHP is not yet validated.1 But, IHP should use the right drug against the right tumor. To enlarge the panel of tumors targeted by IHP, other drug classes, including cytostatic,43 virus-mediated gene transfer,44 meta-melphalan (e-mail: eric.savier@psl.ap-hop-paris.fr).

REFERENCES


